Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Case Report

T-Cell/Myeloid Mixed-Phenotype Acute Leukaemia with KMT2A Rearrangement

Ibtisam Abdullah[1*], Monalisa Ntobongwana[1], Helena Cornelissen[1], Zivanai Cuthbert Chapanuka[1] , Leilah Schoonraad[2]

[1]Department of Hematological Pathology, Stellenbosch University, Stellenbosch, South Africa; [2]Department of Pediatric, Stellenbosch University, Stellenbosch, South Africa

ABSTRACT

Mixed Phenotype Acute Leukemia (MPAL) is a rare leukemia subtype arising from hematopoietic pluripotent stem cells. The hallmark of the disease is co-expression of myeloid antigens and B- or T-lymphoid antigens. We discuss an 11-year-old female, who presented with gum hypertrophy, lymphadenopathy and anemia with 84% blasts on peripheral blood examination. Immunophenotyping revealed two blast populations co-expressing markers of both T-cell and myeloid lineages with monocytic differentiation. Cytogenetics showed at (6;11). The diagnosis of T-cell/myeloid MPAL with KMT2A rearrangement was made. Two rare features noted were, the two distinct myeloid and monocytic blast sub-populations and T-cell/myeloid marker co-expression with KMT2A-rearrangement. The KMT2A rearrangement has been associated with B-cell/myeloid mixed phenotypic leukemia however association with T-cell/myeloid mixed phenotype is rare.

Keywords: Acute monocytic leukemia; Flow cytometry; KMT2A-rearrangement, Mixed phenotype acute leukemia; T-cell; Mixed-phenotype acute leukemia

INTRODUCTION

Mixed Phenotype acute Leukemia (MPAL) is a heterogeneous group of rare and poorly differentiated diseases that comprises about 2-5% of All Acute Leukemias (ALL) [1]. MPAL can be classified into MPAL with (9;22), MPAL with KMT2A-rearrangement, B cell/myeloid-Not Otherwise Specified (NOS), T-cell/myeloid-NOS, B/T-lymphoid and, more rarely, as trilineage B-cell/T-cell/myeloid [2]. The T-cell/myeloid phenotype represents 35% of all MPAL [3]. Unlike acute myeloid leukemia with recurrent genetic abnormalities, the role of cytogenetic aberrations such as KMT2A-rearrangement in the pathophysiology of MPAL remains unclear.

Here we report a case of a patient with T-cell/myeloid acute leukemia with monocytic differentiation and KMT2A-rearrangement.

CASE REPRESENTATION

A previously well 11-year-old female was admitted with a two-week history of gum hypertrophy and gum bleeding. Physical examination revealed cervical lymphadenopathy (largest; 4 cm), hepatomegaly; 4 cm below the costal margin and no splenomegaly. Serology for Hepatitis A, B and C, HIV, and CMV virus were all negative. Pertinent hematological investigations showed anemia with a hemoglobin concentration of 10.4 g/dL, a leucocytosis of 114 × 109/L and a normal platelet count of 140 × 109/L. The peripheral blood film revealed 84% blasts with an apparent dual blast population. Population 1 comprised large blast cells with abundant grey-blue cytoplasm, fine granules, regular to kidney-shaped nuclear contours, dispersed immature chromatin and 1-2 prominent nucleoli, resembling promonocytes. Population 2 comprised medium-sized blast cells with a moderate amount of basophilic cytoplasm, fine granules and some with thin Auer rods, convoluted nuclear borders, immature chromatin and prominent nucleoli. (Figures 1 and 2). The bone marrow aspirate was hypercellular with 90% blasts.

Correspondence to: Dr Zivanai Cuthbert Chapanuka , Department of Hematological Pathology, Stellenbosch University, Stellenbosch, South Africa, Tel: 270845843583; E-mail: Zivanai@sun.ac.za

Received: June 02, 2021, **Accepted:** June 16, 2021, **Published:** June 23, 2021

Citation: Abdullah I, Ntobongwana M, Cornelissen H, Chapanduka ZC, Schoonraad L (2021) T-Cell/Myeloid Mixed-Phenotype Acute Leukaemia with KMT2A Rearrangement. J Leuk. 9:257

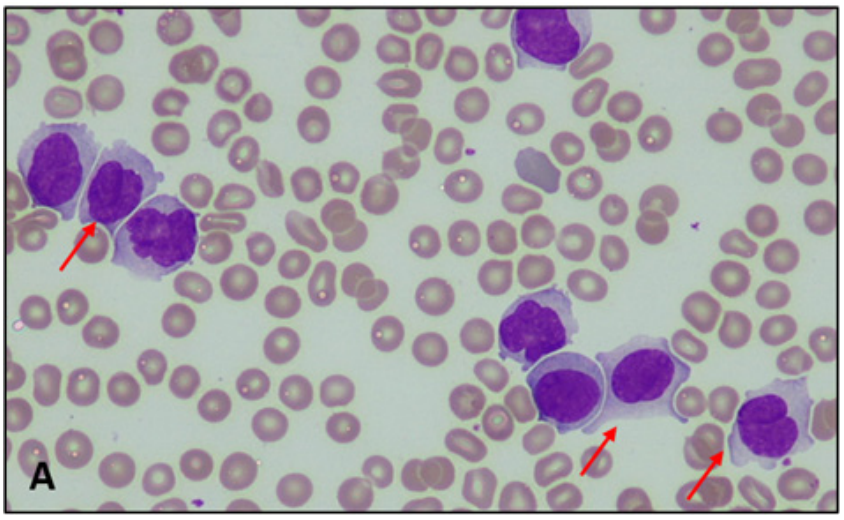

Figure 1: Promonocytes-like blasts, large blast cells with abundant grey-blue cytoplasm, fine granules, regular to kidney-shaped nuclear contours, dispersed immature chromatin.

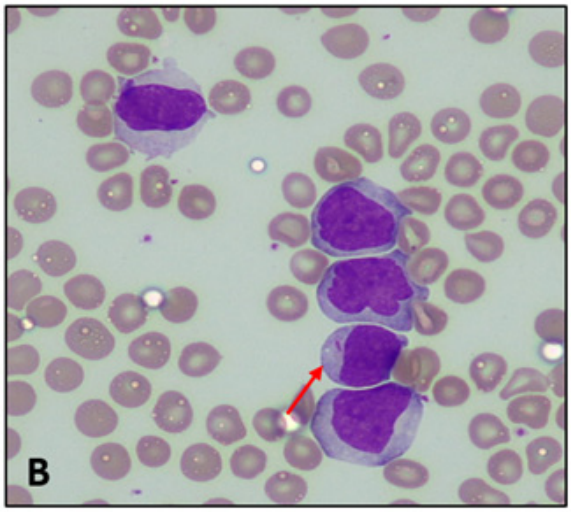

Figure 2: Myeloid blasts with Auer rods.

A four-colour multiparameter flow cytometry analysis was performed using the BD-Lyric® flow cytometer [4]. Immunophenotyping revealed the existence of a unique population of blast cells that were positive for both myeloid and T-lineage differentiation. The blasts exhibited co-expression of specific T-cell lineage marker, cytoplasmic CD3(cCD3), and myeloid markers including cytoplasmic myeloperoxidase (cMPO), CD117, bright CD33 and CD13 with a subset exhibiting monocytic differentiation including CD11c, CD14, CD36 and CD4. This monocytic subset appears separate from the myeloblast component. A subset analysis was performed and it showed two separate populations of myeloblasts. The first population expresses specific T-cell lineage marker, cCD3, together with early myeloid markers including CD117, CD13, CD33, cMPO. This population lacks expression of monocytic markers (CD14, CD11b, CD11c) and shows aberrant expression of CD56 and CD4. The second population expresses cCD3 together with monocytic markers including CD14, CD11b and CD11c with negative cMPO, CD117 and CD13. The blasts were also positive for CD45weak, partial CD34, CD38 and partial myeloperoxidase. All the blasts were negative for surface CD3, CD10, CD19, CD8, nuclear TdT and cytoplasmic CD79a (Figure 3).

Fluorescence in Situ Hybridization (FISH) showed KMT2A-rearrangement and was negative for t(9;22), t(8;21) and inversion 16. Karyotyping demonstrated a reciprocal translocation between the long-arms of chromosomes 6 and 11. Breakage and reunion occurred at bands 6q27 and 11q23 with an exchange of material distal to these breakpoints. This translocation results in the formation of the KMT2A/AFDN fusion-gene (Figure 4). Based on these results a diagnosis of T-cell/myeloid mixed-phenotype acute leukemia with KMT2A rearrangement was made in accordance with the WHO classification 2016 [2].

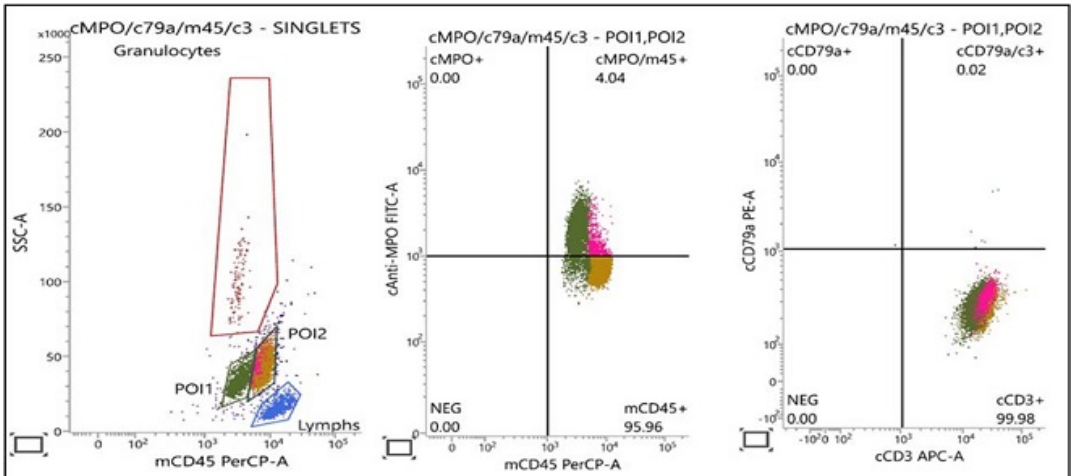

Figure 3: Flow cytometry scatter plot.

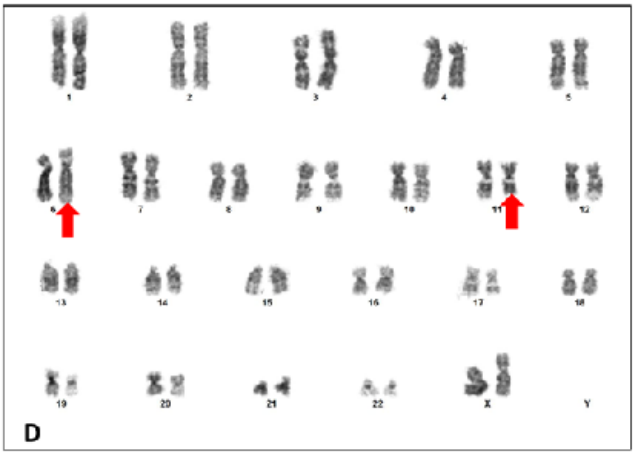

Figure 4: Karyotyping showing reciprocal translocation between the long-arms of chromosomes 6 and 11.

The patient was initially treated on a cytoreductive AML pre-phase regimen (6-thioguanine and cytarabine) due to her high white cell count and provisional flow cytometry results showing monocytic differentiation. On this regimen, her white cell count continued to rise and when the final flow cytometry report indicated that cCD3 was convincingly positive in all blast population, her chemotherapy regimen was switched to a high risk Acute Lymphoblastic Leukemia (ALL) regimen. Her day 7 bone marrow biopsy showed a minimal response to the chemotherapy with a decrease in leucocytes from 114 to 471 x 109/L but more than 40% blasts remained on the aspirate and trephine. The patient completed intensive induction chemotherapy and experienced grade 3-4 hematological toxicity. A repeat bone marrow biopsy at day 28 of therapy showed morphological remission, but the KMT2A-rearranegment was found indicating that molecular remission was not achieved. She was then switched to an ALL regimen for refractory or relapsed disease. A hematopoietic stem cell transplant is planned for when she is in full remission.

RESULTS

The 2016 WHO classification of mixed phenotype acute leukemia is based on the expression of specific lineage markers [2]. The cytoplasmic CD3 (cCD3) is the T-cell-specific marker, while myeloid markers are either MPO or two or more monocytic markers specifically CD11c, CD14, CD64 or lysozyme. In this case, the blast population partially expressed myeloperoxidase by flow cytometry, suggesting a myeloid origin. On the other hand, the blasts clearly showed co-expression for cCD3 and the associated monocytic markers, CD11c and CD14, which characterises this case as T-cell/myeloid mixed phenotype acute leukemia with monocytic differentiation in accordance with the WHO classification 2016 [2]. Based on morphology and flow cytometry the blast population was subdivided into two populations. The first population showed monocytic morphology and immunophenotyping with co-expression of cCD3. The second population showed myeloid blast population with Auer rods and positive for MPO, a marker which is usually negative or dim in monocytic blasts with co-expression of cCD3.

Mixed phenotypic acute leukemia with KMT2A-rearrangement is a rare entity [1]. MPAL with KMT2A-rearrangement, usually associated with B-cell/myeloid phenotype and the presence of T-cell/myeloid phenotype with KMT2A-rearrangement, is rare [3]. The presence of two subpopulations that co-express T/Myeloid markers even more rare. Matutes, et al. published a series of 100 cases of MPAL, where they reported 35 cases with T-cell/myeloid phenotype, only four cases with CD14 expression and 13 cases showing positivity for lysozyme. A single case had KMT2A-rearrangement [3].

The possibility of concomitant expressions of T-cell and monocytic differentiation antigens in the same blast population is hard to explain using the classical model of hematopoiesis. There are many potential mechanisms for the development of acute leukemia with combined T-lymphocytic and myeloid differentiation. These include mutation of myeloid or multipotent progenitors resulting in T-cell differentiation, mutation of T-cell progenitor with myeloid potential and mutations that cause loss of T-cell commitment in T-cell restricted progenitors [5]. The theory of mutations deriving T-cell differentiation in myeloid or multipotent progenitors could explain the myeloid and T-cell expression, however, the presence of a monocytic components which develops at a late stage of myeloid differentiation cannot be fully explained by this theory. Alternative mechanisms may be responsible for the development of this leukemia. In the early stages of hematopoiesis, the separation of the B-cell and T-cell lymphoid lineages may occur prior to the loss of myeloid/macrophage potential. However, it is challenging to explain the existence of both T-cell and monocytic involvement in the same leukemic cells [6]. Moreover, immature intra-thymic T-cell precursors, at early double negative stages of differentiation, retain multilineage differentiation potential, which suggests their direct derivation from hematopoietic stem cells [7,8]. Studies have demonstrated that immature T-cell progenitors give rise to macrophages and neutrophils that harbour TCR gene rearrangement in vivo [6,7]. Therefore, we could hypothesize that T-cell/monocytic leukemia cells could arise from an immature T-cell precursor before the loss of myeloid differential potential.

DISCUSSION

Alejandro, et al. suggested acute myeloid/T-cell lymphoblastic leukemia as a new diagnostic entity and that defining the detailed molecular mechanisms may lead to the improvement of therapy for this subgroup of leukemia [5].

In general, leukemias with KMT2A-rearrangement, are more common in pediatric, than adult populations [2]. Acute myeloid leukemia with KMT2A-rearrangement, previously known as MLL-rearrangement, is seen in 9-12% of pediatric Acute Myeloid Leukemia (AML) compared to 2% of adult AML cases [2,9]. Mixed-phenotype acute leukemia with KMT2A-rearrangement is rare but its relatively more common in infants. The KMT2A-rearrangement confers a poor prognosis [2]. Approximately 10% of all leukemias harbour KMT2A translocations and the translocation involving 11q23 generate in-frame fusions of the MLL gene to more than 80 different partner genes [10]. KMT2A-rearrangement frequently involve fusion partners in the ENL (Eleven Nineteen Leukemia)-associated protein (EAP) complex. This rearrangement accounts for 90% and 70% of KMT2A-rearranged lymphoblastic leukemia and acute myeloid leukemia, respectively [11].

KMT2A proteins play an important role in the regulation of transcription [11]. A general concept is that in terms of gene expression profiling the fusion proteins lead to overexpression of genes. In KMT2A leukemias the overexpressed genes are the HOX cluster genes and the HOX cofactor MEIS1. In hemopoietic cells, KMT2A translocation results in oncogenic fusion proteins that recruit H3K79 methyltransferase. These changes cause epigenetic changes that promote an oncogenic pattern of gene expression resulting in dysregulation of transcription, driving a subset of infantile and adult leukemias [12]. Signalling pathways such as the RAS/RAF pathway are also affected. A significant association between pediatric KMT2A-rearrangement and N- or K-RAS mutations has been reported. This causes enhancement of RAS pathway signalling and results in oncogenesis [11,12].

Mixed phenotype acute leukemia has an inferior outcome in comparison to AML and ALL. The median overall survival reported is 15-18 months [13]. There is still uncertainty regarding the best approach to treatment of MPAL. This uncertainty is mainly due to rare incidence, difficulties in classification and the lack of prospectively collected data concerning therapeutic outcomes. However, limited studies suggest that higher remission rates are achieved with ALL-like induction regimens and allogeneic transplantation in first remission [13]. Our patient is receiving ALL regimen for refractory or relapsed disease and full remission was not achieved at the time of writing. An allogeneic bone marrow stem transplant is planned as soon as she is in first remission due to the high-risk immunophenotype and cytogenetics of her leukemia.

CONCLUSION

This case report discusses a rare presentation of MPAL. It highlights the diagnostic as well as therapeutic challenges of such cases. Knowledge about the association between KMLT2A-rearrangement and T-cell/myeloid mixed phenotype acute leukemia with monocytic differentiation is still limited.

ACKNOWLEDGEMENTS

The authors thank Liezl van Schalkwyk for technical assistance with flow cytometry, Dr Erica-Mari Nell for assisting flow cytometry interpretation and Daphne Tylor for performing and interpreting FISH and cytogenetic analysis.

REFERENCES

1. Aribi A, Bueso-Ramos C, Estey E, Estrov Z, O'Brien S, Giles F, et al. Biphenotypic acute leukemia: A case series. Br J Hematol. 2007;138(2): 213-216.
2. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. Revised 4t. France: International Agency for research on cancer (IARC); 2016.
3. Matutes E, Pickl WF, Veer MVNT, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: Clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood. 2011;117(11): 3163-3171.
4. BD FACSLyric - BD Biosciences , BD Biosciences-US.
5. Gutierrez A, Kentsis A. Acute myeloid/T-lymphoblastic leukemia (AMTL): a distinct category of acute leukemias with common pathogenesis in need of improved therapy. Br J Hematol. 2018;180(6): 919-924.
6. Bell JJ, Bhandoola A. The earliest thymic progenitors for T cells possess myeloid lineage potential. Nature. 2008;452(7188): 764-700.
7. Wada H, Masuda K, Satoh R, Kakugawa K, Ikawa T, Katsura Y, et al. Adult T-cell progenitors retain myeloid potential. Nature. 2008;452(7188): 768-72.
8. Coustan-Smith E, Mullighan CG, Onciu M, Behm FG, Raimondi SC, Pei D, et al. Early T-Cell Precursor Leukemia: A Subtype of Very High-Risk Acute Lymphoblastic Leukemia Identified in Two Independant Cohorts. Lancet The. 2010;10(2): 147-156.
9. Byrd J, Mrózek K, Dodge R, Carroll A. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100(13): 4325-4336.
10. Winters AC, Bernt KM. MLL-rearranged leukemias- An update on science and clinical approaches. Front Pediatr. 2017;5(2): 11-13.
11. Rao RC, Dou Y. Hijacked in cancer: the MLL/KMT2 family of methyltransferases. Nat Rev Cancer. 2015;15(6): 334-346.
12. Marschalek R. Mechanisms of leukemogenesis by MLL fusion proteins. Br J Hematol. 2011;152(2): 141-154.
13. Wolach O, Stone RM. Mixed-phenotype acute leukemia: Current challenges in diagnosis and therapy. Curr Opin Hematol. 2017;24(2): 139-45.