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Lysine (K)-specific methyltransferase 2A (KMT2A) rearrangements among Iraqi *de novo* acute myeloid leukemia

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Abstract:

BACKGROUND: The classification of acute myeloid leukemia (AML) has evolved extensively over the last 20 years significantly, impacting the diagnosis and prognosis of the patients. The lysine (K)-specific methyltransferase 2A (KMT2A) gene, which has more than 80 gene fusions, is present in approximately 10% of all leukemias. Most KMT2A rearrangements are associated with adverse prognosis and need heavy chemotherapy protocol upfront.

OBJECTIVE: This study aims to study the prevalence of KMT2A gene fusion among Iraqi patients with AML and its association with clinical and hematological parameters and patients' outcomes.

PATIENTS, MATERIALS, AND METHODS: A prospective cohort study conducted between December 2020 and May 2022 enrolled 115 Iraqi adults newly diagnosed with AML at the Hematology Unit of Baghdad Teaching Hospital. The patients were also monitored at this facility during the study period. Genetic rearrangements were detected using the Leukemia Q-Fusion Screening Kit through Real-Time Quantitative Reverse Transcription PCR (RT-qPCR) analysis.

RESULTS: KMT2A rearrangements were identified in 23 (20%) patients. The most common was t(10;11) which presented in 15 (13%) patients, followed by t(9;11) in 5 (4.3%) patients and t(11;17) in 3 (2.6%) patients. Patients with KMT2A rearrangements were significantly older and more likely to have splenomegaly. At 1-month posttreatment, they had significantly lower red blood cell counts and hemoglobin levels and higher blast percentages. Only 4.3% achieved complete remission (CR) compared to 76.1% without KMT2A rearrangements, with a significantly higher mortality rate (30.4% vs. 5.4%, $P = 0.0001$). Regarding the treatment response, no significant differences were observed among the different fusion types of KMT2A rearrangements.

CONCLUSION: KMT2A rearrangements are more prevalent among Iraqi AML patients compared to the global trend and are associated with older age, higher rates of splenomegaly, poorer hematological recovery, and worse outcomes, regardless of the KMT2A rearrangement fusion type.

Keywords:

Acute myeloid leukemia, Iraqi acute myeloid leukemia, lysine (K)-specific methyltransferase 2A, lysine (K)-specific methyltransferase 2A rearrangements

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid precursor cells, leading to impaired hematopoiesis and bone marrow (BM) failure. The classification and management of AML have evolved significantly with advancements in our understanding of the genetic landscape of the disease, which plays a crucial role in diagnosis, prognostication, and treatment stratification.[1]

In the last 20 years, the classification system for AML has undergone significant changes,

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profoundly influencing both the diagnosis process and prognostic outcomes.[2] The "lysine (K)-specific methyltransferase 2A" (KMT2A), also known as mixed lineage leukemia, is associated with a unique subset of leukemia, particularly through chromosomal translocations, which are characterized by more than 80 gene fusions.[3]

Less than 10% of all types of leukemias had the KMT2A rearrangement. Among these, the t(9;11)(p22;q23) translocation is classified as carrying an intermediate risk, while all other KMT2A rearrangements are associated with an adverse prognosis.[1] Treatment strategies for AML with KMT2A translocations often involve high-dose chemotherapy in Iraq and possibly hematopoietic stem cell transplantation since it is associated with less favorable outcomes.[4]

The prevalence and impact of KMT2A rearrangements vary globally, influenced by factors such as ethnicity, age, and environmental exposures.[5] Despite their recognized significance, there are limited data on the prevalence and clinical impact of these rearrangements in specific populations, including Middle Eastern cohorts. Understanding these genetic variations is crucial for developing targeted treatment approaches and improving outcomes for AML patients. In the Iraqi population, genetic studies have been relatively underrepresented, and the specific characteristics of AML, including the frequency and types of KMT2A rearrangements, remain underexplored.

In a previous study, we identified the common KMT2A rearrangements among Iraqi patients, and in this study, we aimed to study the prevalence of KMT2A gene fusion among Iraqi patients with AML and its association with clinical and hematological parameters and patients' outcomes.

Patients, Materials, and Methods

This cohort study is part of previously published studies[4,6] which is a prospective cohort study conducted between December 2020 and May 2022 and enrolled 115 Iraqi adults newly diagnosed with AML at the Hematology Unit of Baghdad Teaching Hospital.

The inclusion criteria for the study were patients aged 18 years and above who were newly diagnosed with AML, confirmed by blood film and flow cytometry, and were within 1 week of treatment initiation. The exclusion criteria included patients who had undergone allogeneic transplantation, pregnant women, and individuals with a history of cancer (or myelodysplastic syndrome).

The patients were also monitored at this facility during the study period. Genetic rearrangements were detected using the Leukemia Q-Fusion Screening Kit through RT-qPCR analysis. Ethical approval for this study was obtained from College of Medicine's Ethical Committee at the University of Baghdad.[4]

Prior to initiating the research, the study protocol obtained ethical approval from the Ethical Committee of the College of Medicine at the University of Baghdad, ensuring compliance with all ethical standards throughout the study. Patient consent was obtained prior to inclusion in the study.

All patients received the standard chemotherapy protocol, based on hospital protocol. The assessment of response was conducted following the initial cycle of induction, 28 days postinduction. The complete response (CR) (BM blasts <5%, circulating blast absence, and no blasts with Auer rods, without extramedullary disease, as well as the absolute neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L). Blast persistence (BP) after the first induction is defined as BM blasts $\geq 5\%$ at any time after day 13 of the first induction but before the next chemotherapy cycle.[2]

Statistical analysis

Data were analyzed using descriptive and inferential statistical methods. Continuous variables were summarized as means and standard deviations, while categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using the independent *t*-test for continuous variables, analysis of variance test for more than 2 variables, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate.

Results

Out of 115 *de novo* AML patients, KMT2A rearrangements were identified in 23 (20%) patients. The t(10;11) was the most common KMT2A rearrangement, found in 15 (13%) patients, followed by t(9;11) found in 5 (4.3%) patients. The t(11;17) rearrangement was identified in 3 (2.6%) patients [Figure 1].

The comparison between patients with and without KMT2A rearrangements showed a significant difference in age and the presence of splenomegaly. Patients with KMT2A rearrangements were older and more likely to have splenomegaly ($P < 0.05$). No significant differences were observed in sex distribution, smoking status, or the presence of hepatomegaly [Table 1].

The hematological parameters of AML patients with and without KMT2A rearrangements at baseline and 1 month later showed no significant differences in red

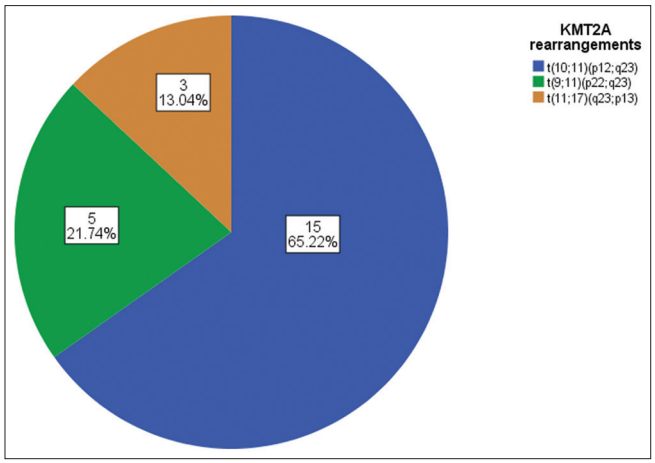

Figure 1: Lysine (K)-specific methyltransferase 2A rearrangement frequency. KMT2A = Lysine (K)-specific methyltransferase 2A

blood cell (RBC) count, hemoglobin levels, white blood cell (WBC) count, platelet count, or blast percentage between the two groups at baseline. However, at the 1-month mark, significant differences have been observed, and the patients with KMT2A rearrangements had a lower RBC count ($P = 0.042$) and low Hb level ($P = 0.012$) compared to those without the rearrangements. In addition, the blast percentage was significantly higher among KMT2A rearrangement patients ($P = 0.0001$). There were no significant differences in WBC and platelet counts at 1 month [Table 2].

Response assessment

The treatment response and outcomes of AML patients based on the presence or absence of KMT2A rearrangements showed that among patients with KMT2A rearrangements, only 1 (4.3%) achieved complete response (CR), while 15 (65.2%) experienced blast persistence (BP), and 7 (30.4%) died. In contrast, patients without KMT2A rearrangements had significantly better outcomes, with 70 (76.1%) achieving CR, 17 (18.5%) experiencing BP, and 5 (5.4%) dying, with a significantly better response among patients without KMT2A rearrangements in comparison to those with KMT2A rearrangements ($P = 0.0001$) [Table 3].

The comparison of the demographic and clinical characteristics and treatment responses of AML patients with different KMT2A rearrangements: t(10;11), t(9;11), and t(11;17) is given in Table 4.

Patients with the t(10;11) ($n = 15$) had a mean age of 59.8 ± 12.2 years, with 60% of females and 40% of males. Among these patients, 13.3% were smokers, 60% had splenomegaly, and 33.3% had hepatomegaly. In terms of response, 6.7% achieved complete remission (CR), 73.3% had BP, and 20% died.

Table 1: Demographics of acute myeloid leukemia by lysine (K)-specific methyltransferase 2A rearrangements

Variables	KMT2A rearrangements		*P*
	Yes (*n*=23)	No (*n*=92)	
Age, mean±SD	58.1±16.3	41.9±16.9	0.0001
Sex, count (%)			
Female	14 (60.9)	54 (58.7)	0.85
Male	9 (39.1)	38 (41.3)	
Smoking, count (%)			
Yes	3 (13)	16 (17.4)	0.76
No	20 (87)	76 (82.6)	
Organomegaly, count (%)			
Splenomegaly (yes)	11 (47.8)	21 (22.8)	0.017
Hepatomegaly (yes)	6 (26.1)	14 (15.2)	0.29

KMT2A=Lysine (K)-specific methyltransferase 2A, SD=Standard deviation

Table 2: Hematological parameters at baseline and 1 month after treatment by lysine (K)-specific methyltransferase 2A rearrangements

Hematological parameters	KMT2A rearrangements		*P*
	Yes (*n*=23)	No (*n*=92)	
Baseline (mean±SD)			
RBC	3.09±1.65	2.77±1.43	0.35
Hb	7.68±1.79	7.82±2.53	0.8
WBC	4.74±3.20	5.96±3.79	0.15
PLT	72±47	83±74	0.49
Blast %	65±16	66±19	0.67
1 month (mean±SD)			
RBC	3.06±0.94	3.72±1.20	0.042
Hb	9.3±2.3	10.7±2.1	0.012
WBC	6.05±2.56	6.32±2.79	0.72
PLT	143±70	151±55	0.61
Blast %	38±22	8±17	0.0001

KMT2A=Lysine (K)-specific methyltransferase 2A, SD=Standard deviation, RBC=Red blood cell, WBC=White blood cell, Hb=Hemoglobin, PLT=Platelet

Table 3: Response assessment by lysine (K)-specific methyltransferase 2A rearrangements

Response	KMT2A rearrangements		*P*
	Yes (*n*=23), *n* (%)	No (*n*=92), *n* (%)	
CR	1 (4.3)	70 (76.1)	0.0001
BP	15 (65.2)	17 (18.5)	
Death	7 (30.4)	5 (5.4)	

KMT2A=Lysine (K)-specific methyltransferase 2A, CR=Complete remission, BP=Blast persistence

Among the group with t(9;11) ($n = 5$), the mean age was 48.2 ± 9.3 years, with 40% of females and 60% of males. None of these patients were smokers or had splenomegaly or hepatomegaly. In terms of response, none achieved CR, 60% had BP, and 40% died.

In the group with *t* (11;17) translocation ($n = 3$), the mean age was 72.3 ± 10.6 years, and all patients were female. Among these patients, 33.3% were smokers, 66.7% had splenomegaly, and 33.3% had hepatomegaly.

Table 4: Demographic and clinical characteristics of lysine (K)-specific methyltransferase 2A rearrangement acute myeloid leukemia by fusion type

Variable	KMT2A rearrangements			*P*
	t(10;11) (*n*=15), *n* (%)	*t*(9;11) (*n*=5), *n* (%)	*t*(11;17) (*n*=3), *n* (%)	
Age, mean±SD	59.8±12.2	48.2±9.3	72.3±10.6	0.076
Sex				
Female	9 (60)	2 (40)	3 (100)	0.24
Male	6 (40)	3 (60)	0	
Smoking				
Yes	2 (13.3)	0	1 (33.3)	0.39
Splenomegaly				
Yes	9 (60)	0	2 (66.7)	0.052
Hepatomegaly				
Yes	5 (33.3)	0	1 (33.3)	0.32
Response				
CR	1 (6.7)	0	0	0.53
BP	11 (73.3)	3 (60)	1 (33.3)	
Death	3 (20)	2 (40)	2 (66.7)	

KMT2A=Lysine (K)-specific methyltransferase 2A, CR=Complete remission, BP=Blast persistence, SD=Standard deviation

In terms of response, none achieved CR, 33.3% had BP, and 66.7% died.

There were no statistically significant differences between the three groups in terms of age, sex, smoking status, presence of splenomegaly, or hepatomegaly ($P > 0.05$). The response rates, including death, also did not show a statistically significant difference among the groups ($P = 0.53$). This suggests that while there are variations in demographics and clinical features among the different KMT2A rearrangement groups, these differences are not statistically significant.

Discussion

The rearrangement of KMT2A and its various types have been associated with poorer outcomes and are considered independent adverse prognostic factors for *de novo* AML, as well as therapy-related AML.[7]

In this study, KMT2A rearrangements were identified in 20% of *de novo* AML patients in Iraq, which is significantly higher than the prevalence reported globally (3%–6% of *de novo* AML adult patients).[8-10] This discrepancy in prevalence may be due to differences in sample size and the time periods of the studies; for example, the HARMONY study[6] included patients from the late 19th century onward. Importantly, the higher prevalence in our study may indicate a possible regional or genetic predisposition among the Iraqi population that merits further investigation.

In our study, the t(10;11) translocation was the most frequent KMT2A rearrangement, accounting for 65% of cases, followed by t(9;11) at 22%. This contrasts with findings from the HARMONY study,[8] where t(9;11) was the most common KMT2A rearrangement at 49%, and both t(10;11) and t(11;17) were present in only 5% of cases each. Similarly, a study by Issa *et al*.[11] reported t(9;11) in 57% of participants, with no identification of t(11;17) among their AML patients. Another study by Bill *et al*.[12] found t(9;11), t(10;11), and t(11;17) present in 44%, 8%, and 3% of cases, respectively. These discrepancies in the frequency of KMT2A rearrangements could be attributed to several factors, including differences in patient populations, sample sizes, and study methodologies.

In addition, the higher frequency of t(10;11) and the lower frequency of t(9;11) compared to other studies suggest that there may be distinct biological or environmental factors at play in the Iraqi cohort. Furthermore, the variation in the types of KMT2A rearrangements has important clinical implications. The t(9;11) translocation is typically associated with intermediate risk, whereas others, such as t(10;11), are generally linked to poorer prognosis.[2,13] Our findings of a higher prevalence of t(10;11) underscore the need for aggressive treatment strategies and close monitoring of AML patients with this translocation in Iraq.

Our study found that patients with KMT2A rearrangements were significantly older, with a mean age of 58.1 years, compared to 41.9 years in patients without these rearrangements ($P = 0.0001$). Despite the global trend where KMT2A rearrangements are often seen in younger patients, specifically among patients younger than 60 years old, our results for patients with KMT2A rearrangements are still seen in younger age group.[14,15] The reason for patients with KMT2A rearrangements being older than other Iraq AML cohort is due to the fact the AML patients in Iraq presented younger than global trend and this has been described in our previously published research.[4]

In addition, splenomegaly was more common in patients with KMT2A rearrangements (47.8% vs. 22.8%, $P = 0.017$). The presence of splenomegaly among AML patients aligns with existing literature.[16] However, the existing literature has not extensively studied the association between KMT2A rearrangements in AML and splenomegaly. The significant presence of splenomegaly in the KMT2A group might be related to advanced age or the aggressive nature of the disease associated with KMT2A rearrangements.

Despite the lack of significant differences in hematological parameters at baseline between patients with and without KMT2A rearrangements, significant differences emerged at the 1-month mark. Patients with KMT2A rearrangements exhibited poorer hematological recovery, as evidenced by lower RBC counts, lower

hemoglobin levels, and higher blast percentages. This trend toward poorer hematological recovery underscores the aggressive nature of AML with KMT2A rearrangements. Interestingly, a study by Issa *et al*.[11] found a significantly higher percentage of blasts at baseline among patients with KMT2A rearrangements. This finding aligns with our observation of higher blast percentages at 1 month posttreatment, suggesting that KMT2A rearrangements contribute to a more aggressive disease course from the onset. The elevated blast percentages and poorer hematological recovery observed in our study highlight the aggressive biology of AML with KMT2A rearrangements, which is aligned with the literature, indicating that these genetic abnormalities are linked to worse outcomes.[17]

The treatment response and outcomes of AML patients in our study were consistent with the well-documented adverse impact of KMT2A rearrangements. Patients with KMT2A rearrangements had significantly poorer outcomes and response rates compared to those without these genetic abnormalities. These findings align with existing literature that associates KMT2A rearrangements with a more aggressive disease course and poorer prognosis.[18,19]

In addition, the poor outcomes and increased mortality in these patients may also be attributed to the aggressive chemotherapy regimens used, which can lead to prolonged neutropenia. This prolonged neutropenia, in turn, elevates the risk of opportunistic infections, such as invasive fungal infections (IFIs), a major cause of mortality in AML patients receiving intensive induction chemotherapy.[20,21]

Interestingly, despite the classification of t(9;11) as an intermediate-risk translocation, our study found no significant differences in treatment response among the different KMT2A rearrangement types ($P = 0.53$). This suggests that all types of KMT2A rearrangements in our cohort are linked to adverse outcomes, highlighting the uniformly poor prognosis associated with these genetic alterations regardless of the specific translocation involved. This was aligned with HARMONY study[6] that showed no significant differences in response between t(9;11) AML patients and rest of KMT2A rearrangements.

While previous studies, such as Krauter *et al*.,[22] have shown superior response rates for the t(9;11) rearrangement compared to other KMT2A rearrangements, Bill *et al*.[10] linked better responses specifically to patients under 60 years old with t(9;11) *de novo* AML. Furthermore, Chen *et al*.[19] found improved outcomes for patients with t(9;11) in a cohort that included both younger and older patients.

Despite the small sample size in our study used for comparing different types of KMT2A rearrangements, and the heterogeneity of other studies regarding the treatment response and outcome for t(9;11), reclassifying t(9;11) to the adverse group may be necessary. This would ensure that these patients receive more attention and appropriate treatment, reducing the risk of poorer outcomes. The variability in response and outcomes across different studies highlights the need for a more cautious and aggressive treatment approach for patients with the t(9;11) rearrangement, recognizing the potential for adverse prognosis even in cases previously considered intermediate risk.

The study had several limitations, most notably the small patient sample, which makes generalizing the results challenging. In addition, a longer follow-up period is essential to comprehensively assess outcomes and draw more robust conclusions.

Conclusion

Our study reveals a higher prevalence of KMT2A rearrangements in Iraqi AML patients compared to global trends, with a particularly high occurrence of the t(10;11) translocation. These rearrangements are associated with older age, higher rates of splenomegaly, poorer hematological recovery, and worse treatment outcomes. Despite the global classification of t(9;11) as an intermediate-risk translocation, our findings suggest that all KMT2A rearrangements, including t(9;11), contribute to adverse prognostic outcomes in our cohort. These results highlight the need for more aggressive and tailored treatment strategies for patients with KMT2A rearrangements.

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Conflicts of interest
There are no conflicts of interest.

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