MULTILINEAGE DYSPLASIA IN IRAQI KURDS WITH ACUTE MYELOID LEUKEMIA: A RETROSPECTIVE STUDY ON 105 PATIENTS

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ABSTRACT

Background: Acute Myeloid leukemia (AML) with multilineage dysplasia (MLD) is an important subcategory of acute myeloid leukemia, which has been reported to have prognostic importance. No studies have addressed this category of AML in Iraq Kurds, so this study was initiated.

Subject and Methods: A total of 105 patients diagnosed as Acute Myeloid leukemia over 10 years were reassessed. They have a median age of 40 and a male: female ratio of 1.02:1. The reassessment included re-evaluation of their clinical and hematological records, as well as re-evaluation of their peripheral blood and marrow smears for multilineage dysplasia. The study also included assessing any correlations between various clinical and hematological parameters and the presence of MLD.

Results: Multilineage dysplasia was documented in 35.3% of cases. The dysplasia was bilineage in 23.8% and trilineage in 11.4%. The most frequent dysplastic changes were hypogranular granulocytes, pseudo-pelger-huet anomaly, and mono-lobated megakaryocytes, seen in 46.6%, 29.5% and 20.9% respectively. The dysplasia was encountered in most frequently in M5 and M6 morphological subtypes, while it was absent in the M3 subtype, a finding which was significant (p =0.001). When the latter subtype was excluded from evaluation, it was found that patients with MLD were less likely to have organomegaly, more likely to have leukopenia, platelets < 20x10⁹/l, blast <20% in peripheral blood or <60% in bone marrow than those with no MLD, although none was significant.

Conclusions: Multilineage dysplasia is frequently encountered in Iraqi Kurds with AML and seen in all morphological subtypes except M3, and its presence needs to be documented in bone marrow reports on new AML cases. Further prospective studies preferably including cytogenetics to evaluate outcome in AML-MLD versus AML without it, needs to be initiated.

Keywords: AML, Multilineage Dysplasia, Kurds, Iraq.

Acute myeloid leukemia (AML) is a collection of neoplastic blood disorders characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood or other tissues¹. It is the most common acute leukemia in adults, accounting for about 80% of cases in this age group². The annual incidence of AML is approximately 2.4 per 100,000, and it increases progressively with age, with a median age at diagnosis of 67 years and male predominance in most countries³. Acute myeloid leukemia with multilineage dysplasia (AML-MLD) was introduced by the WHO in 2001 as a new entity and defined by presence of 20% or more peripheral blood (PB) or bone marrow (BM) blasts with morphological features

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of myelodysplasia or a prior history of a myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN)⁴. The emphasis in this classification was mainly on morphological dysplasia, though in more recent WHO classifications, the addition of cytogenetics as a defining criterion was made, and the term AML with myelodysplasia-related changes (AML-MRC) was introduced⁵, ⁶. The importance of recognizing this entity as a distinctive entity of AML is that several studies have demonstrated that it exhibits a significantly worse clinical outcome compared to AML without associated myelodysplasia⁵.

In view of the absence of previous studies on multilineage dysplasia in Iraqi Kurds with AML, this study was initiated aimed at determining the frequency of this subgroup among AML patients from two teaching hospitals. Furthermore, we also aimed to determine any clinical and hematological correlations of AML of the latter subgroup.

MATERIALS AND METHODS

A total of 105 patients diagnosed in the period between 2007 and 2017 based on morphology of blood film and bone marrow, supplemented by cytochemistry and/or immunophenotyping were retrospectively assessed at Azadi and Hevi teaching hospitals –Duhok, Kurdistan/Iraq. The assessment included reviewing clinical and hematological records. The peripheral blood and marrow smears were re-evaluated for morphological subtyping. Moreover, they were scrutinized for the presence and extent of dysplastic changes in erythroid, myeloid and megakaryocytic elements to determine whether they qualify for being considered AML with multilineage dysplasia. The criteria for such designation require the presence of dysplasia in at least 50% of the cells in at least two BM cell lines. Dyserythropoietic features were defined as more than 50% dysplastic features in at least 25 erythroblasts. Dysgranulopoietic features include three or more neutrophils with hyposegmented nuclei (pseudo-Pelger–Heutz anomaly), and hypogranular or agranular neutrophils (more than 50% of 10 or more neutrophils). Dysmegakaryopoietic features were defined as three or more megakaryocytes being micronuclear, multiseparated nuclear or large mononuclear⁵.

The study was approved by the Kurdistan commission of medical specialization, Erbil, Kurdistan-Iraq. The statistical analysis utilized the chi square for categorical variables and the t test for the continuous ones. A p value of < 0.05 was considered significant.

RESULTS

General characteristics

The enrolled patients had ages ranging between 1.3 and 80 years (median 40 years) and included 87% adults (>15 years). There were 53 males and 52 females (male to female ratio of 1.02:1.0. Clinically, the most common features were pallor, bleeding manifestations, fever, splenomegaly and hepatomegaly, seen at frequencies of 95.2%, 36.2%, 29.5%, 20.9%, and 13.3% respectively. Blood counts revealed anemia in 90.4%, thrombocytopenia in 98%, leukocytosis in 59%, while leucopenia was noted in 23.8%. Bone marrow was hypercellular in 88.5% of cases, normocellular in the rest.
The application of the FAB classification on our cases revealed that the most frequent subtype was M2, followed M3, and M4, while the least was M6 (Table 1).

### Table 1: AML morphological subtypes and their association with MLD.

| FAB Classification | Overall (no.105) | AML-MLD (no. 37) | p-Value |
|--------------------|------------------|------------------|---------|
| M0                 | 12 (11.4)        | 5 (41.7)         | 0.6200  |
| M1                 | 18 (17.1)        | 7 (38.9)         | 0.722   |
| M2                 | 31 (29.5)        | 14 (45.2)        | 0.169   |
| M3                 | 19 (18.1)        | 0 (0)            | 0.001   |
| M3V                | 2 (1.9)          | 0 (0)            | 0.294   |
| M4                 | 17 (16.2)        | 6(35.3)          | 0.996   |
| M5                 | 5 (4.8)          | 4(80.0)          | 0.095   |
| M6                 | 1 (1.0)          | 1 (100.0)        | 0.173   |

AML with Myelodysplasia
Dysplastic changes noted in enrolled patients varied in frequency, it involved one cell line in 13 (12.4%), two in 25 (23.8%), and three in 12 patients (11.4%). The most frequent dysplastic change was hypogranular granulocytes seen in 46.6%, followed by pseudo- Pelger- Hüet neutrophil abnormality in 29.5% and monolobed megakaryocytes in 20.9%. Other dysplastic changes are outlined in Table 2, and illustrated in Figures 1 & 2.

When the M3 subtype was excluded from evaluation, because of the absence of dysplasia, and the remaining 84 cases were analyzed, it was found that there were no significant differences in age, sex, or clinical presentation between those with MLD and those without it. Despite the lower rates of hepatomegaly (13.5% vs. 21.3%), splenomegaly (21.0% vs. 25.5%) and lymphadenopathy (8.1% vs. 14.1%), in those with dysplasia, however this was not significant (p values of 0.36, 0.68 and 0.54 respectively). As for the peripheral blood findings, and although leucopenia <4 x10^9/L and platelets <20 x 10^9/L were more frequent in dysplasia patients, neither was significant (p=0.167 and 0.62 respectively) (Table 3). Furthermore, peripheral blood blasts of less than 20 and bone marrow blasts less than 60 were more frequent among those with MLD, though again these were insignificant (Table 3).
Table 3: Comparison between some hematological parameters in AML with multilineage dysplasia versus those without it.

| Parameter                  | NON MLD | MLD | P Value |
|----------------------------|---------|-----|---------|
| Hemoglobin g/dl (mean± SD) | 76.97±15.54 | 76.22±15.50 | 0.192 |
| HB <10 g/dl                | 39 (83) | 27 (73) | 0.269 |
| WBC x10^9/L (mean±SD)      | 35.42±37.14 | 35.37±34.40 | 0.995 |
| WBC<4x10^9/L               | 5 (10.6) | 8 (21.6) | 0.167 |
| WBC>11x10^9/L              | 35 (57.4) | 27 (73) | 0.877 |
| Platelets x10^9/L (mean±SD)| 51.31±36.58 | 72.43±79 | 0.108 |
| PLT<150 x10^9/L            | 47 (100) | 34 (91.9) | 0.163 |
| PLT<20 x10^9/L             | 7 (14.9) | 7 (18.9) | 0.62 |
| PB % Blasts (mean± SD)     | 55.75±24.85 | 57.33±25.42 | 0.588 |
| PB % Blasts <20%           | 3 (8.3) | 4 (12.1) | 0.466 |
| BM % of blasts (mean±SD)   | 59.97±21.37 | 56.05±25.62 | 0.452 |
| BM% of Blasts <60%         | 20 (42.5) | 17 (45.9) | 0.756 |

Figure 2: Shows (a) Blast + proerythroblast in the only AML-M6 case, (b) binucleated erythroid, (c) Internuclear bridge and (d) multi nucleated erythroid precursor.
DISCUSSION

The general characteristics of our patients are to a great extent consistent with previous reports from Iraq\(^7,\ 8\). Our median age of 40 years is not unexpected since our series includes both children and adults and it has been documented that patients from this part of the world are generally younger at presentation than their Western counterparts\(^3,6,9\). The male to female ratio approaches unity, which is not unique, and has been reported by previous studies from Iraq, USA and Japan\(^7,10,11\), though most other studies report male predominance\(^9\). The distribution of morphological subtypes according to FAB classification is again consistent with previous studies from Iraq\(^7,\ 8\), where M2, M3 and M4 are the most frequent subtypes. The main difference from Western studies, is that the M3 subtype is relatively more frequent in this part of the world, while its contribution in the former countries is much less\(^9\).

Multilineage Dysplasia was identified in 35.3\% of cases, which is relatively intermediate between previous reports from Europe and North America, where figures ranging from 15-48\% have been reported\(^6,12-19\). The variation in these figures is most likely due to variable definitions and strictness of criteria as well as the extent of investigation in different series. The lower figures focused on trilineage dysplasia and did not include bilineage ones as the new definition now necessitates, while the higher figures are

![Figure 2](image_url)

Figure 2: Shows examples of dysplastic features in granulocytic cells and Megakaryocytes (a) Pseudo-pelger neutrophil, (b) hypogranular neutrophil, (c) Multi separated lobes megakaryocytes and (d) monolobed megakaryocyte.
likely due to the inclusion of secondary AML as opposed to denovo AML, and/or the inclusion of cytogenetic studies as recommended in the new version of WHO classifications and the entity AML-MRC rather than AML-MLD as used in our study. In a developing country like ours, and in the absence of routine cytogenetic testing, identifying the latter entity seems to be more realistic at this time. One of the difficulties facing previous observers as well as the current authors and may have led to underestimation of MLD, was the overwhelming marrow infiltration by blasts in many, leaving very limited residual hemopoietic element to evaluate for dysplasia.
The failure to document any association of MLD with age is consistent with several earlier studies\textsuperscript{12, 20, 21}, but is contrary to others which suggested association of MLD with older patients\textsuperscript{6, 22}. From the clinical aspect, the finding of lower proportions of hepatomegaly/ Splenomegaly/ Lymphadenopathy (though insignificant) is consistent with some earlier studies\textsuperscript{12}, and with the notion that AML-MLD has a lower blast burden than denovo AML without it. The higher rates of blasts <20% in blood and <60% in marrow in those with MLD in our series is consistent with the latter notion. The association of MLD with the morphological subtypes M6, M5 and to a lesser extent in M4, M2, M1 and M0, but not with M3 is again similar to that reported in the literature\textsuperscript{12, 23}. Some investigators have found that morphological MLD on its own, is associated with worse prognosis regardless of cytogenetic changes, which supports the importance of identifying AML-MLD as

attempted in our series\textsuperscript{6,14,15,18,19}. Though others, found that MLD is often linked to prognostically unfavorable AML cytogenetic profiles, but does not retain on its own independent prognostic effect\textsuperscript{13,20-22}. So this topic remains much contested\textsuperscript{24}, and it would have been quite interesting if the current study included evaluation of survival and remission induction data, but we were limited by the retrospective nature of the study.

In conclusion, it was found that among our patients with AML, MLD is quite frequent and further prospective studies including preferably cytogenetic and molecular studies to document the significance of this observation through assessment of overall survival, event free survival and remission induction results are necessary.

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ثوختة
طهورينين تتخين شانتيي بين هاسماجور لدك لموردي عيراقيي بين ك ذابجيشي خوييئ دجوري ماليويدي ددور هى. ظاكولينيا ثاوناتيي لستر 105 نخوشان

ثيشكي: ثابجيشي خوييئ دجوري ماليويدي ددور يا كو طهورينين هاسماجوريين تتخين شانتيي نيكى دجوري طرنتين تتخيشي خوييئ دجوري ماليويدي كو طرنتينيا وى دناشيييو باشناخي دا. هيش ظاكولين ل هارما كوردستانى نهاتينه كرن لستر ظل باباى لفوا نغ ظاكولينة هاته ناتهجامان.

ريكين ظاكوليني: سترجامى 105 نخوشان هاته هاسماجورينتغوزه كو ثابجيشي خوييئ ددور هى ل سترانسركى 10 سالان دا. تيكرايي ذى وان 40 دال بوون و ريدا نبى بو مى 1.02 بو 1 بو. دوباره هاسماجورينتغوزه طان نخوشان هاته كرن بو نوماريين وان بين كليكيي و بين خوينى هاروسا هاسماجورينتغوزه تاكيكرين خوييي وماناتي هايى ب طهورينين شانتيي بين هاسماجور. دتى ظاكوليني دا كوماكا هاتينيديا هاته دياركرن ناظيرات داتانى كليكيي و بين خوينى و هيهونا طهورينين شانتيي بين هاسماجور.

نأجام: طهورينين شانتيي بين هاسماجور هاته دييت لنطف 35.3% نخوشان كي ل 23.2% دولاياتي بوون و ل M5 و ديارتمى و 11.4% سى ليابانى بوون. نغ طهورينية ل ثاباريا جورين نخوشنى بوون و تتر ل جوري M5 و ديارتمى مورسي بون دهوى زانسيي طة (p=0.001). ذنى جوري M3 دياربوو كو نخوششى طهورينين هاسماجور هى كيمتر نوشى مارونيىان هنوك نخدامين لخواى دين و تتر نوشى كيمبونا تتى خوينى بين ستى و تتروىي خوىئي ب بيتراودرى دجارتل نخوششى طهورينين هاسماجور ناى.

دكراناجام: طهورينين شانتيي بين هاسماجور مشى دهيه دييت لنطف نخوششى ثابجيشي خوييئ دجوري ماليويدي ددور لدكى و هامى جور دهيه دينى نبى M3. هيهونا طهورينا نتني حبة نوكومينى كرن ل تافيكرى ماندى هامى و تتر نغيدية ظاكولينيين نائيبيي بيبيه كرن سيماىشى شانى و هاتسماجورينى دكراناجاما لنطف نخوششى طهورينى، هاسماجور هى بيتراودرى دجارتل وان بين نغ طهورينى نخ.
الخلاصة

خلل التنسج المتعدد في الكورد العراقيين المصابين بسرطان الدم النخاعي الحاد: دراسة أسترجاعية

خلفية والأهداف: سرطان الدم النخاعي الحاد ذو النمو الشاذ المتعدد الطبقات هو فئة فرعية هامة من سرطان الدم النخاعي الحاد، وقد تم تسجيله لأهميته كذكير تكيني. لم يتم أي دراسة من هذا القبيل عن هذه الفئة في إقليم كردستان، لذا بدأت هذه الدراسة.

طرق البحث: تم إعادة تقييم ما مجموعه 105 مريض تم تشخيصهم بأنهم سرطان الدم النخاعي الحاد على مدى 10 سنوات. وبلغ متوسط العمر 40 سنة، ونسبة الذكور: الإناث 1:0.2. وشمل تقييم السجلات السريرية والدموية إعادة تقييم فحوصات الدم المحيطي ومسحات النخاع لبحث عن النمو الشاذ المتعدد الطبقات. وشملت الدراسة مقارنة الارتباطات بين اختلاف المعايير السريرية والدموية مع وجود النمو الشاذ المتعدد الطبقات.

النتائج: تم توثيق النمو الشاذ المتعدد الطبقات في 35.3% من الحالات. وكان خلل النمو الشاذ الثنائي في 23.8% والثلاثي في 11.4%. كانت التغيرات المتكررة المتضمنة هي الخلايا المحبخة قليلة الفصوص، شذوذات في الاسم، والوراثة. أحيانًا الفصوص، وجلت في 46.5%، 29.5% و 20.9% على التوالي. وقد وجد النمو الشاذ في معظم الأنواع الفرعية البحرية في حين كان مقفولا في النوع الفرعي M3. ولن يكون على الأرجح في M6 و M5. ولكن على الأرجح في M5. و P = 0.001. (P = 0.001). عندما تم استبعاد النوع الفرعي الأخير من التقييم، وجد أن المرضى الذين يعانون من النمو الشاذ المتعدد الطبقات كانوا أقل احتمالا أن يكون لديهم تضخم عضوي، ولكن من المرجح أن يكون لديهم نقص الكريات البيض، الصفاحات الدموية أقل من 9x10^9/μl، خلايا الدم الحبيبي أقل من 20% في الدم المحيطي أو 60% في نخاع العظام مقابل مع أولئك الذين ليس لديهم النمو الشاذ المتعدد الطبقات.

الاستنتاجات: أن نسبة عالية من حالات سرطان الدم النخاعي الحاد في دهوك تشهد وجود نمو شاذ متعدد الطبقات ويشمل هذا جميع الأصناف الشكلية باستثناء M3. ويشتمل تقييم وجود النمو الشاذ المتعدد الطبقات في تقارير سرطان الدم النخاعي الحاد، ومن الأفضل أن تشمل الدراسات المرتبطة في الوقاية الخلوي للتنبيه نتائج هذا السرطان الحاد ذو النمو الشاذ المتعدد الطبقات مقابل نتائج سرطان الدم الحاد بدون هذا النمو.