

Original Research Article

CD 117: Lineage assigning marker in acute myeloid leukemias

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ABSTRACT

Background: Acute Myeloid Leukemia (AML) is a malignancy of the cells of myeloid series characterized by the rapid growth of Myeloblasts. The diagnosis of AML is established by demonstration of more than 20% of the blood and/or bone marrow by leukemic myeloblasts. Immunophenotyping is one of the most useful tool for the confirmation, lineage assignment and subtyping of leukemias. This study was aimed to phenotype and classify acute leukemias by flow cytometry using commonly used markers for leukemia diagnosis and to establish whether CD 117 can be considered as a lineage specific marker in diagnosis and subclassification of AML.

Methods: Flow Cytometric Immunophenotyping was employed for the study. The myeloid antibodies employed in AML in our study included - CD117, CD11c, CD13, CD15, CD33, CD34, CD36, CD41, CD65 and MPO.

Results: In our study AMLs constituted 46% of all acute leukemias. CD117 positivity was seen in 86.56% of the French American British (FAB) category of AML. The blasts gated using CD45 v/s SSC revealed variable expression of CD34, CD13 and CD33. The expression of CD117 was consistent particularly in AML-M0, AML-M1 and AML M2.

Conclusions: CD117 is virtually a myeloid blast marker with a high sensitivity, specificity and positive predictive value. Among the various myeloid markers like cMPO, CD13, CD33 and CD117, it is just CD117 that has got a tremendous reproducibility in AMLs. Besides CD117 is a surface marker unlike MPO thus easier to process, time saving and less prone to nonspecific binding.

Keywords: Acute myeloid leukemia, CD117, Immunophenotyping, Myeloblasts

INTRODUCTION

Acute Myeloid Leukemia (AML) is a malignancy of the cells of myeloid series which is characterized by the rapid growth of Myeloblasts that build up in the bone marrow and interfere with the production of normal blood cells. In AML a differentiation arrest in combination with other mutations disrupt genes controlling proliferation resulting in uncontrolled growth of an immature clone of cells, leading to AML.¹ Within the past few years, novel

genetic mutations have been identified in essentially all types of AML and many of these have proved to be powerful prognostic factors.^{2,3} According to the widely used World Health Organisation (WHO) criteria, the diagnosis of AML is established by demonstrating involvement of more than 20% of the blood and/or bone marrow by leukemic myeloblasts, except in the three best prognostic forms of acute myeloid leukemia with recurrent genetic abnormalities [AML with t(8;21), AML with inv(16), and AML with PML-RAR α] in which the presence of the genetic abnormality is diagnostic

irrespective of blast percentage.^{4,5} The patient can present from leukopenia to hyperleucocytosis with an elevated blood blast count.⁶

Cytochemical stains on blood and bone marrow smears are often helpful in the distinction of AML from ALL and in subclassification of AML. The combination of a Myeloperoxidase (MPO) or Sudan Black (SBB) and a Non Specific Esterase (NSE) stain will provide the desired information in most cases. Immunophenotype is one of the most useful tool for the identification of leukemia subtypes.⁷⁻¹⁰ The flow cytometric immunophenotyping helps in confirmation of Acute leukemia and to assign a specific lineage and also in detection of aberrant immunophenotypic profiles which can be of prognostic importance and it also helps in detecting minimal residual disease (MRD). The monoclonal antibodies commonly employed in immunophenotyping of Acute Myeloid Leukemias include - CD117, CD11c, CD13, CD15, CD33, CD34, CD36, CD41, CD65 and MPO. CD117 is normally expressed by bone marrow hematopoietic precursors and can be detected in the myeloid lineage until the promyelocyte stage and in the erythroid lineage until the pro-erythroblast stage.¹¹ CD117 is preferentially associated with the AML-M0, AML-M1 and AML-M2 subtypes. In AML-M3 (Acute Promyelocytic Leukemia) subtype it is often positive, especially in the M3-variant form. In AML, CD117 is highly expressed on 60-80% of myeloblasts and c-KIT is mutated in approximately 5% of all AML cases.¹²

METHODS

The study was conducted on patients with acute leukemia diagnosed in the Department of Hematology, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), a super speciality Hospital in Soura, Srinagar, Jammu and Kashmir, India. The study was conducted to study the diagnostic utility of Immunophenotypic analysis of acute leukemia by Flow cytometry at SKIMS, Srinagar from January 2015 to August 2017.

In the study conducted, the cases that were of particular interest were the ones which were not discernible on morphology/cytochemistry as Acute Myeloid Leukemia or Acute Lymphoblastic Leukemia (FAB- AML-M0, M7, T-ALL, B-ALL, ALL-L2 etc.) Patients of all age group were taken up for the study. Venous blood sample (2 to 3 ml) collected in an EDTA vacutainers and Bone marrow aspiration samples (2 to 3 ml) collected in Lithium Heparin/EDTA vacutainers were taken. The total leucocyte count of samples was performed using LH-750 series CBC analyzer from Beckman and Coulter. These samples were immediately processed so that prompt diagnosis and treatment was ensured to the patient. However, if delay ensued due to any reason or the need for putting additional antibodies, the samples were stored at 2-8°C in a refrigerator and processed within 24 hours.

Staining procedure

For surface antigen staining, 100 micro liters of the blood/bone marrow sample was stained with the desired quantity of fluorescently labeled monoclonal antibody (mAb) and incubated in the dark at room temperature (RT) for 20 minute, lysed with 500 µl Optilyse, a lysing solution, and incubated at room temperature for an additional 10 minutes and given 2 to 3 washings and sample was acquired. For detection of cytoplasmic antigens like CD79a, MPO permeabilization reagent was used. The Flow Cytometric Immunophenotyping at our centre was done on Beckman Coulter Navios® and data analyzed using Kaluza® software.

On Flow Cytometry, CD45 versus Side Scatter (CD45/SSC) was used for gating of leukemic blasts. The observations that leukemic blasts usually show less intense CD45 expression compared with normal blood leukocytes has simplified gating strategies for leukemia analysis.¹³ AML cells were identified by their expression of cytoplasmic MPO, CD13 and CD33 and CD117.

RESULTS

A total of 250 cases were diagnosed as acute leukemia during a period of 2 years with 115 cases of AML (46%); the incidence being higher in elderly males. The results showed a good correlation of morphology with that of flow cytometry. A standard panel of monoclonal antibodies manufactured by Beckman Coulter were employed (Table 1).

The blasts were gated using CD45 v/s SSC which revealed a variable expression of CD34, CD13, and CD33. However, the expression of CD117 was consistent particularly in AML-M0, AML-M1 and AML-M2 (Figure 1).

Among the 115 cases diagnosed on flow, agreement with morphological diagnosis (FAB classification) was found in 67 cases. 48 cases could not be well categorized into any FAB sub-group. This was because Bone Marrow Aspiration was not done in all cases and also in many scantily particulate marrow very less number of cells were available for analysis and in a few cases of AML with t(8;21) the blasts on flow cytometry were less in number. Therefore, it wasn't possible to categorise these cases in any FAB group. Based on morphology though many cases were suggestive of AML, with Auer rods seen in few cases and MPO positivity in many. The diagnostic dilemma was in cases with the absence of Auer rods or Non-contributory special stains. It was seen in our study that CD117 on Flow Cytometry was a very useful marker with a high sensitivity. The study conducted at our centre showed a majority of cases of AML being positive for CD117. Among the various myeloid markers which included cMPO, CD13, CD33 and CD117, it was CD117 that showed a tremendous reproducibility in AMLs with a highest percentage of

blasts with CD117 positivity seen in AML-M2 (82%) followed by AML-M0 (78%), AML-M1 (74.7%), AML-

M7 (66%), AML-M3 (57%), AML-M4 (36%) and AML-M5 (20%).

Table 1: Antibody combinations with associated fluorochromes.

| Fluorochrome | FITC | PE | ECD | PC5.5 | PC7 | APC | APC-AF700 | APC-AF750 |
|--------------|------------------------------------|------------------------|------|------------------------|--------------|----------------------|----------------------|------------------------|
| Antibody | CD7 CD20 CD64 CD65 MPO | CD33 CD79a CD117 | CD45 | CD10 CD61 HLA-DR | CD13 CD19 | CD19 CD33 CD41 | CD5 CD22 CD11c | CD14 CD56 CD235a |

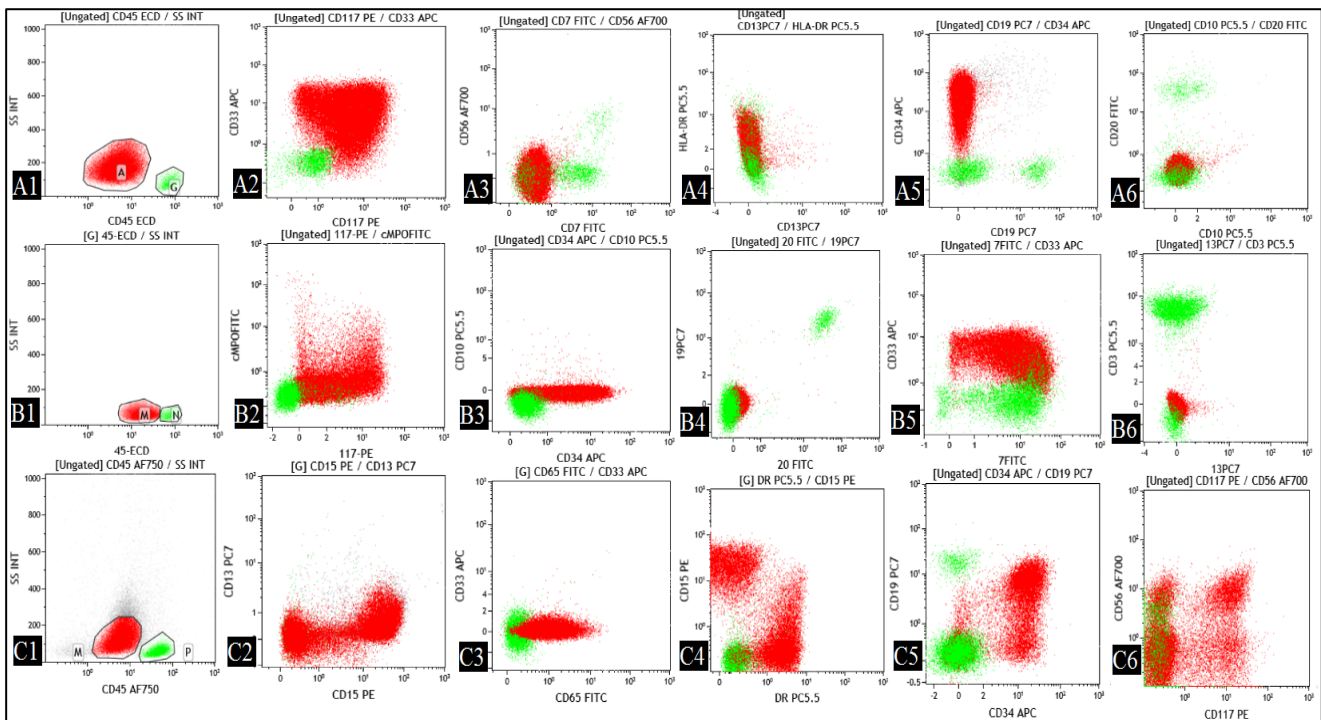


Figure 1: A1 to A6. Acute Myeloid Leukemia with Minimal Differentiation. Plots show positivity for CD33, CD34, CD117, HLA-DR. The blasts are negative for CD13 and MPO (not shown). B1 to B6. Acute Myeloid Leukemia without Maturation. Plots show positivity for CD7, CD33, CD34, CD117; a fraction of Blasts showed positivity for MPO. C1 to C6. Acute Myeloid Leukemia with Maturation. Plots shows positivity for CD15, CD19, CD34, CD56, CD65 and CD117. Interestingly this case is positive for CD19 which was aberrantly expressed here. This was a case of AML with t(8;21) where aberrancy of CD19 is seen.

Table 2: Expression of CD117 and MPO using flow cytometry vis a viz FAB-AML subgroups.

| FAB classification | Total Cases | %age of Blasts expressing | |
|--------------------|-------------|---------------------------|------|
| | | CD117 | MPO |
| AML-M0 | 7 | 78 | - |
| AML-M1 | 9 | 74.7 | 33.8 |
| AML-M2 | 4 | 82 | 66 |
| AML-M3 | 19 | 57 | 64 |
| AML-M4 | 16 | 36 | 20 |
| AML-M5 | 11 | 20 | 42 |
| AML-M6 | 0 | - | - |
| AML-M7 | 1 | 66 | - |

cMPO on the other hand showed a low sensitivity with many cases of AML being negative for MPO especially AML-M0 and AML-M7 (Table 2). Overall in the 67 cases of the AML-NOS (FAB), 58 cases showed a positivity for CD117 (86.56%) with expression pattern ranging from dim to bright. In the 48 cases of AML which could not be categorised under any FAB group the expression of CD117 was seen in 46 cases (95.83%).

DISCUSSION

The AML as per FAB classification system and WHO, NOS subgroup are categorised into the following categories:

- AML-M0: AML with minimal differentiation/undifferentiated.
- AML-M1: AML without maturation.
- AML-M2: AML with maturation.
- AML-M3: Acute promyelocytic leukemia (now categorized as AML with PML-RAR α).
- AML-M4: Acute myelomonocytic leukemia
- AML-M5: Acute Monocytic/Monoblastic leukemia.
- AML-M6: Pure erythroid leukemia
- AML-M7: Acute megakaryoblastic leukemia.

Though to differentiate these FAB subgroups from each other morphology and cytochemistry is often useful

especially in AML-M2, AML-M3, AML-M4 and AML-M5. In cases where the nature of the blasts is indistinguishable morphologically especially when the blasts are large, having a high nuclear cytoplasmic ratio, fine nuclear chromatin with ≥ 2 prominent nucleoli with agranular cytoplasm. Such morphology can be seen in Lymphoblasts (FAB- ALL-L2) as well as in Type 1 Myeloblasts (Myeloblasts are morphologically divided into three types. In type 1, the morphology is same as described as above, thus reminiscent of FAB: ALL-L2 Lymphoblasts. Type 2 Myeloblasts have few granules and Type 3 have significant granulation). In such a situation it is impossible to differentiate the two, especially when no Auer rods are seen or special stains are non-contributory (i.e MPO positivity in $<3\%$ of blasts). In such a situation these blasts are labelled as AML-M0/ALL-L2. AML- M1 is diagnosed on the basis of blasts either showing Auer rods or $>3\%$ blasts showed MPO positivity on cytochemistry with a maturing component constituting $<10\%$ of Non Erythroid Cells (NECs) counted on Bone Marrow Aspiration smears. AML-M2 is diagnosed based on presence of frequent Auer rods and majority of blasts showing MPO positivity on Cytochemistry and maturing component constituting $>10\%$ of Non Erythroid Cells (NECs) counted on bone marrow aspiration smears. On the other hand, cases of APLM, AML-M4 and AML-M5 have a characteristic morphology and immunophenotypic profile (Figure 2).

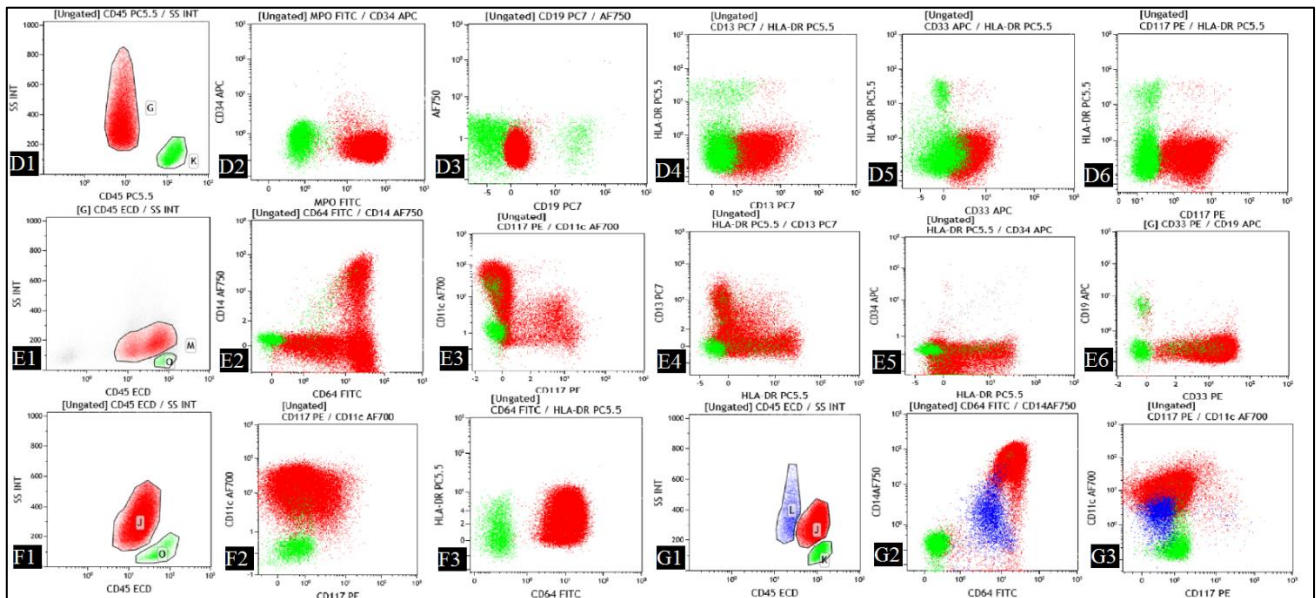


Figure 2: D1 to D6. Acute Promyelocytic Leukemia. Plots showing tear drop pattern on CD45/SSC with positivity for MPO, CD117 and characteristic CD34 and HLA-DR negativity. E1 to E6. Acute Myelomonocytic Leukemia. Plots showing cell extending from dim CD45 to the Monocytic zone on CD45/SSC with a characteristic trail pattern on CD14/CD64 scatterplot with positivity for CD11c, HLA-DR, CD13, CD33 and CD117. F1 to F3. Acute Monoblastic Leukemia. The plots show positivity for CD11c, CD64, HLA-DR, CD36 (not shown) with a subset of cells showing CD117 positivity. CD14 was negative as all the cells were Monblasts where there is absence of CD14. G1 to G3. Acute Monocytic Leukemia. The plots show a prominent zone in monocytic zone with a co-expression of CD14 and CD64 along with expression of CD11c.

The problem therefore lies in differentiating those blasts that are morphologically as well as on cytochemistry indistinguishable. Such blasts are seen in T-ALL, B-ALL, AML-M0, MPAL, AML-M7 etc. The classical description of M7 blasts having cytoplasmic blebbing is not seen always, so cannot be differentiated on morphology. It is important for proper differentiation of the blasts as the treatment protocols are different for various leukemias. This differentiation is achieved using Flow cytometric immunophenotyping of these blasts. As per WHO, based on certain antigens present on the blasts we can distinguish blasts into myeloid or lymphoid (Table 3).

Table 3: Lineage assignment based on WHO.

| Leukemia type | Markers required to be positive |
|---|--|
| B-ALL | CD19 strong with dim expression of any one- CD10/cCD22/cCD79a (or) CD19 dim with strong expression of any two- CD10/cCD22/cCD79a |
| T-ALL | Cytoplasmic CD3 |
| AML | Cytoplasmic MPO |
| Acute Monocytic or Monoblastic Leukemia | Any two of the following- CD4/CD14/CD36/CD64/NSE/CD68 etc. |
| Acute Megakaryoblastic Leukemia | CD41/CD61/CD36/CD71 |

MPO is considered to be a lineage specific marker for Myeloids as per WHO which is a cytoplasmic marker. There is no mention of CD117 in WHO lineage assignment. The purpose of the study was to justify the role of CD117 as a lineage assigning marker in AMLs along with MPO which has got certain limitations.

CD117 is virtually a myeloid blast marker with a high sensitivity, specificity and positive predictive value with lower negative predictive value.¹⁴⁻¹⁷ In a study conducted by Pomerantz A et al, where they recruited 331 patients and calculated sensitivity of CD117 for AML and found to be 85.88% which was comparable with our study (86.56).¹⁸ Present study showed a higher number of cases showing CD117 positivity (86.56%) in comparison to the study conducted by Ahmadi et al, where CD117 positivity was seen in 75 % of AML with none of the cases of ALL showing positivity for this marker.¹⁹ Also in their study CD117 was positive in 100 % of M5a cases with no M5b cases being positive for this marker. Present study also showed a higher number of cases with CD117 positivity in comparison to the study conducted by Auewarakul CU et al, where out of 163 AML cases, 67% expressed CD117.²⁰ Bene MC et al, in their study showed c-kit (CD117) was expressed in 741 (67%) AML cases which was lower in comparison to present study.²¹ Though WHO has emphasized on MPO as lineage specific marker for myeloid but MPO on flow has got

certain drawbacks which make it unreliable. Rather MPO on cytochemistry is reliable than on FCM. MPO on FCM is known to show non-specific staining, so extra precaution while reporting is to be exercised to prevent a wrong diagnosis. Also, in a small number of cases of B-ALL, weak MPO positivity by FCM has been noted. It is therefore, important that we have a more reliable marker that is specific/sensitive for myeloids. CD117 answers our queries. Other myeloid markers like CD13 and/or CD33 have got a low specificity as these are known to be infidelity markers and their positivity can be noted in B-ALL, T-ALL, Acute undifferentiated leukemia, blastoid plasmacytic dendritic cell neoplasm etc. So, a mere CD13 or CD33 positivity is not sufficient to prove myeloid nature of blasts. Also, CD15, a myeloid marker does not warrant a myeloblasts. In a study conducted by Newell JO et al, it was highlighted that CD117 is sometimes an essential marker for determining blast lineage when evaluating acute leukemias by flow cytometry. Without CD117, the lack of definitive CD13 and CD33 expression with positive CD19 and CD15 staining seen was more consistent with the leukemic blasts being of B cell rather than myeloid lineage. Indeed, CD19 Positive/CD10 Negative B-lineage acute leukemias with CD15 expression are well described and often have abnormalities involving chromosome q23, e.g., balanced 4:11 translocations.²² Now the question is regarding the specificity of CD117 as myeloid blast marker. As per literature and our experience, CD117 positivity in B-ALL is virtually absent. There have been a mere one or two cases of B-ALL showing CD117 positivity. On the other hand, T- ALL can occasionally show CD117 positivity especially cases with activating FLT3 mutations and in Early T- Precursor ALL (ETP-ALL). But CD117 as a blast marker for T-ALL would hold good only if cytoplasmic CD3 and CD7 and hence other T cell markers are positive. If there is no CD7 positivity, the blasts cannot be T-ALL blasts but are very likely myeloblasts instead. Even if CD7 is positive which is commonly seen as an aberrant antigen in AMLs, the absence of cytoplasmic CD3 will qualify such cases as AML rather than T-ALL. Even if MPO/CD13/CD33 are negative in a suspected case of AML, a mere CD117 positivity will assure you that it is AML provided cytoplasmic CD3 is negative. In one patient in our study flow cytometric analysis revealed just CD117 and CD15 positivity and the rest of the myeloid markers like MPO, CD13 and CD33 were negative. On extensive bone marrow examination an Auer rod was noted. In our institute since the inception of flow cytometry, CD117 positivity has been seen in almost all cases of AML barring few cases which included APML and Acute Monocytic/Monoblastic Leukemia. Besides it is important to note that CD117 is a surface marker whereas MPO is a cytoplasmic marker. The staining of a surface marker is less cumbersome, less laborious and time saving. Within one hour the results are ready in case of surface staining, whereas cytoplasmic staining takes at least two hours. The test can be completed using two tubes only in an 8 color and 2 laser flow cytometer. The

importance of CD117 obviates the need for putting cytoplasmic MPO. If CD117 is positive with expression of CD13 and/or CD33 and CD7 is negative, then the diagnosis is firmly Acute Myeloid Leukemia and no further work-up is required. But in the same case if CD7 is positive, then there is a need to put a cytoplasmic tube for cytoplasmic CD3, if that comes negative then the diagnosis stays AML with an aberrant CD7 expression. And if cytoplasmic CD3 comes positive, then the diagnosis is T-ALL/ETP-ALL and not AML. WHO classification of Acute Leukemias is dependent on cytogenetics and molecular studies but in a setup where these facilities are not available, flow cytometry is an important tool to diagnose AML. Further studies including cytogenetics and molecular studies is recommended for a complete work-up.

CONCLUSION

To summarize CD117 is virtually a myeloid blast marker with a high sensitivity and is expressed by almost all cases of AML. Among the various myeloid markers which include cMPO, CD13, CD33 and CD117, it is just CD117 that has got a tremendous reproducibility in AMLs with an advantage of being a surface antigen unlike MPO. MPO though highly specific for Myeloid lineage has certain limitations with positivity not seen in all AMLs and is a cytoplasmic antigen with cumbersome staining procedure. Therefore, authors conclude in this study that CD117 can be considered as a lineage assigning marker in Acute Myeloid Leukemias along with MPO.

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