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Megakaryocyte in Peripheral Blood Smears – A Report of Two Cases

HARSHITA DUBEY*, AMAR RANJAN†, LAWANYA RANJAN‡, PRANAY TANWAR†, GARIMA JAIN#, CHANDAN KUMAR#

ABSTRACT

Myeloproliferative neoplasm (MPN), a clonal hematopoietic stem-cell disorder, results from the proliferation of one or more hematopoietic series of cells like erythroid, granulocytic or megakaryocytic series. Megakaryocytes (MGK) are large polypoidal cells seen within bone marrow aspirate (BMA) smears. We are presenting here two cases of MGK in peripheral blood smears (PBS), one with MPN and the other in a case of chronic myeloid leukemia (CML) with blast crisis. MGK in PBS is rare and is not always associated with neoplasm. It can be due to increased MGK differentiation due to reactive etiology.

Keywords: Megakaryocyte, myeloproliferative neoplasm, bone marrow aspirate, myeloid leukemia, stem-cell disorder

Myeloproliferative neoplasms (MPN) consist of a group of disorders. It is caused by abnormally excessive growth and proliferation of bone marrow stem cells resulting into production of excessive numbers of one or more types of blood cells (red cells, white cells and/or platelets). These cells are compromised in terms of functions. It is a chronic condition that may remain stable for years or may gradually progress to myelodysplastic syndrome (MDS) or to blastic phase of disease over time.

It is a clonal blood stem-cell disorder, caused by mutation, in DNA of stem cell. It is a rare disease. Most common age group is over 50 years, but can occur in any age group.[1]

Megakaryocytes (MGK) are large cells (50-100 μm) that constitute 0.05% of cell population in human bone marrow.[2] Autopsy studies done on tissue sections show that the normal concentration of MGK in bone marrow are 25-32.5 per 10,000 nucleated cells.[3]

*PhD Student
†Additional Professor
‡Master of Engineering Management, Royal Melbourne Institute of Technology, Melbourne, Australia
#Senior Resident
Lab Oncology, IRCH, AIIMS, New Delhi, India
Address for correspondence
Dr Amar Ranjan
Additional Professor
R. No. 422, Lab Oncology,
IRCH, AIIMS, New Delhi - 110 029, India
E-mail: dr.amarranjan@rediffmail.com

Megakaryocyte is routinely seen in bone marrow aspirate (BMA) smear, not in peripheral blood smear (PBS).

However, presence of MGK in PBS has exceptionally been reported in case reports, most of which have been seen in reactive conditions.[4] We, while working at a cancer hospital, found 2 cases of PBS with MGK in it, one with MPN and the other in a case of chronic myeloid leukemia (CML) with blast crisis.

CASE REPORTS

Case 1

A 59-year-old male presented with mass in left upper abdomen with on and off fever for 12 months. Clinical examination showed hepatosplenomegaly. Routine hemogram showed hemoglobin - 11.6 gm%, total leukocyte count (TLC) - 15.3 × 10^9/L and platelet count - 301 × 10^9/L. PBS showed left shift with myelocytes and metamyelocytes comprising of 25% of all nucleated cells. In the PBS, a well-formed MGK was seen at the tail end of the smear (Figs. 1-3).

BMA was markedly diluted, showed hematopoietic cells of all series with Myeloid: Erythroid (M:E) ratio 8:1, 3% blasts and 1% basophils.

Bone marrow biopsy showed marrow fibrosis. Hematopoietic elements were markedly reduced. No dysplasia was noticed. With the suspicion of CML, *BCR-ABL* was done, which was negative. Chronic myeloproliferative neoplasm (CMPD) was considered.

IJCP SUTRA: "Do not eat white refined carbohydrates."

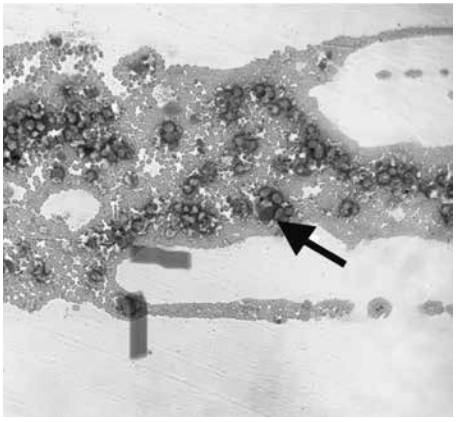


Figure 1. PBS showing megakaryocyte, 10X, Mac-Grunwald Giemsa stain.

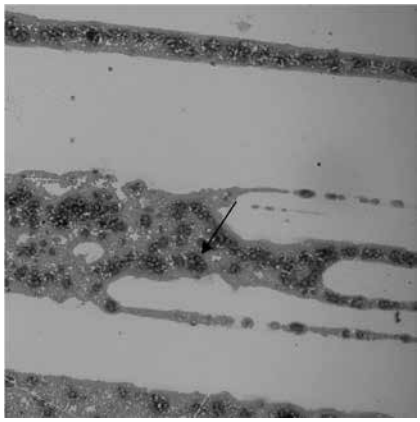


Figure 2. PBS showing megakaryocyte, 4X, Mac-Grunwald Giemsa stain.

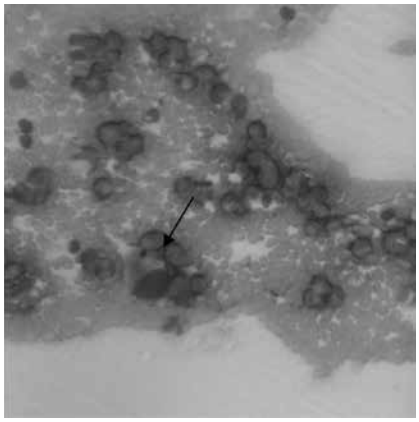


Figure 3. PBS showing megakaryocyte, 20X, Mac-Grunwald Giemsa stain.

Serum level of vitamin B12 was 12.7 (low) (normal range 25-165 pmol/L). During clinical evaluation, it was noticed that the patient was on imatinib 400 mg OD dose for 18 days, but he discontinued it without medical advice for last 15 days. He had complaint of imatinib intolerance (fever and diarrhea). Now, the case was started with imatinib 200 mg/day dose. After 15 days, the patient died.

The case was CMPD, who had two unique presentations: MGK in PBS and imatinib intolerance.

Case 2

A 60-year-old female presented with generalized weakness for 4 months, low-grade fever for 2 months and history of weight loss for 2 months. Pallor, mild hepatosplenomegaly and left cervical lymphadenopathy were present. Hemogram showed TLC - 15 × 10^9/L, hemoglobin - 8.7 gm% and platelet count - 170 × 10^9/L. Differential count of PBS showed blasts (85%) and neutrophil (15%). Interestingly, the PBS showed a well-formed large MGK at the tail of the smear (Fig. 4).

BMA smear examination showed 80% blasts. Bone marrow biopsy showed hypercellular marrow with near total replacement by blasts, which were positive for CD34 and negative for CD3, CD20 and CD138.

Flow cytometry revealed 51% blasts positive for CD19, CD34, CD10, HLA-DR, dim positive for CD79a and TdT and negative for CD45, CD20, CD38, CD33, CD13, CD117, CD64, CD3, CD4, CD5, CD7, CD8 and MPO. Diagnosis of acute lymphoblastic leukemia (ALL) was made and management was started, but no significant improvement was seen. On repeat (thrice) hemogram estimation, it was observed that platelet count was on higher side (>200 × 10^9/L). This raised suspicion of any other associated disease, mainly CML, with blast crisis or Ph-positive ALL. Cytogenetic study revealed chromosome XY, t (9, 22). Reverse-transcriptase polymerase chain reaction (RT-PCR) showed p210 positive. Finally, the diagnosis of CML with blast crisis was considered.

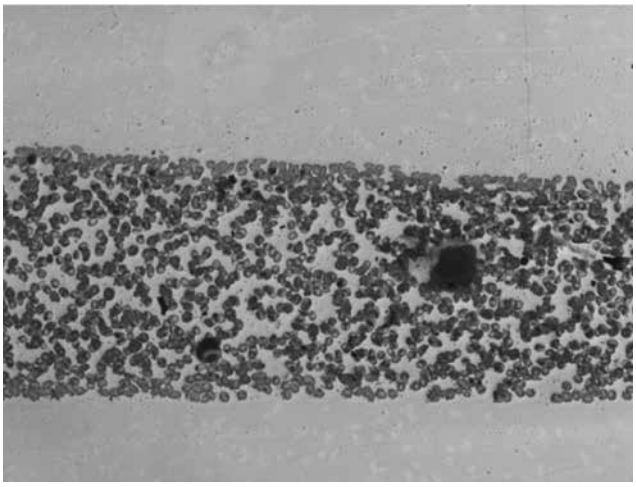


Figure 4. PBS showing megakaryocyte, 20X, Mac-Grunwald Giemsa stain.

A diagnosis of CML with blast crisis was made and treated accordingly.

Till date, the differentiation between CML with blast crisis and Ph-positive ALL is a challenge. On the basis of normal platelet count repeatedly, the diagnosis CML with blast crisis was suggested in this case.

DISCUSSION

Our first case was diagnosed as CMPD, who faced early mortality. So, a confirmatory diagnosis couldn't be made, which required further molecular testing like *JAK-2, MPL,* etc. Bone marrow biopsy showed fibrosis, which raised suspicion of polycythemia vera or

primary myelofibrosis. The two were excluded due to normal level of hemoglobin or platelet count. Essential thrombocythemia (ET) was excluded due to normal platelet count or normal MGK in BMA or bone marrow biopsy. It showed no feature of chronic eosinophilic leukemia. With available studies it may be placed in the category of MPN-Unclassifiable.[5]

MPN–Unclassifiable: It is the least common subtype of MPN. Very little knowledge is available about its incidence, presentations and management. It is diagnosed when an MPN has features of MPN but it does not meet diagnostic criteria of any specific entity. It may overlap two or more entities of MPN.[6]

MPN–Unclassifiable also needs exclusion for the presence of genetic mutation of platelet-derived growth factor receptor alpha (*PDGFRA*), platelet-derived growth factor receptor beta (*PDGFRB*) and fibroblast growth factor receptor 1 (*FGFR1*).

MDS-MPN (chronic myelomonocytic leukemia [CMML]/atypical CML/juvenile myelomonocytic leukemia [JMML]), etc. or MDS was excluded in this case due to absence of atypia. MDS (MDS-SLD/MLD/Ring sideroblasts/excess blasts) was excluded due to absence of atypia. MN with germ line predisposition (*CEBPA*/*DDX41*/*RUNX*/*ANKRD26*/*ETV6*/*GATA2* mutations) is rarely seen and shows positive family history. No such history was found in the patient's family.

Reactive bone marrow response is seen towards alcohol, drug or toxin, folate or vitamin B12 deficiency.[7]

Garg et al, in 2019, showed 4 cases of MGK in PBS. They reported it in 10-year and 14-year-old males. The first presented with reactive thrombocytosis and the other was a burn patient. Other cases were 30-year and 15-year-old females, who presented with thrombocytopenia. The first was positive for dengue serology and the other case was suffering from *Plasmodium vivax* infection. None of their cases had hepatosplenomegaly or evidence of hematological neoplasm.[4]

Ku et al (2017) has shown MGK in PBS in a case of ET that progressed to post-ET myelofibrosis. Platelet count was within normal limit. They proposed an unclear clinical significance for the finding of MGK in PBS.[8]

Erber et al (1987) have shown circulating MGK in PBS in cases of aggressive type of myelodysplasia.[9]

MGK in PBS may be seen in thrombocytosis, thrombocytopenia or with normal platelet count. It may not be associated with hematological disorder. Possibly, it has no clinical significance; however, it requires more study.

In our second case, MGK in PBS may be a presentation of CML in which blast crisis may be the first presentation.

CONCLUSION

Detection of MGK in PBS is rare and it is not always associated with neoplasm. It can be due to increased MGK differentiation due to reactive etiology. Its importance in prediction of any underlying disease needs study on more cases.

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