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# MYELOPROLIFERATIVE NEOPLASMS-A FOUR YEAR STUDY AT A TERTIARY CARE HOSPITAL

Pathology

**Dr Poonam Nanwani*** Assistant professor , Department of Pathology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh*Corresponding Author

**Dr Rohini Bhaskar Kunder** Senior Resident, Department of Pathology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh

**Dr. Nidhi Sharma** Demonstratror, Department of Pathology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh

**Dr. Sativan Khatri** Demonstratror Department of Pathology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh

## ABSTRACT

**Introduction-** Myeloproliferative neoplasms are a group of stem cell disorders characterized by overproduction of mature white cells, red cells or platelets. Diagnostic challenges remain due to phenotypic mimicry of MPNs, failing specificity of BM morphology . **Objective-**Aim of this study is to provide practical approach , how to evaluate MPDs based on the clinical, histological and molecular genetic findings. **Material and methods-** A retrospective study was conducted from January 2019 to January 2023 in the department of pathology. A total of 22 cases of MPN were studied and diagnosis was made based on the clinical features, laboratory features including the peripheral smear, bone marrow aspirate, bone marrow biopsy and molecular genetic studies. **Results –**Out of total 22 cases,16 cases were of Chronic myeloid leukemia (CML), two cases were of Juvenile myelomonocytic leukemia , one case each of Polycythemia Vera, Chronic Neutrophilic leukemia ,Chronic Eosinophilic leukemia , Essential thrombocythemia. CML cases showed BCR-ABL1 positivity. Chronic eosinophilic leukemia was positive for PDGFRA rearrangement while negative for PDGFRB gene. **Conclusion-** Diagnosis of MPNs is a challenge as there is overlap of the clinical and laboratory findings. In this study we included clinical, bone marrow morphology and molecular features to define disease entities and this multimodal approach forms the basis of diagnosis.

## KEYWORDS

Myeloproliferative Neoplasm (MPN) , Chronic Myeloid Leukemia (CML) , Chronic Eosinophilic Leukemia (CEL) , Chronic Neutrophilic Leukemia (CNL)

## INTRODUCTION-

Myeloproliferative neoplasms are progressive in nature and exhibit transition from one disease to another over a period of time and may result in bone marrow failure due to myelofibrosis or transformation to acute blast phase in terminal stage[1]. Diagnostic challenges remain due to phenotypic mimicry of MPNs, failing specificity of BM morphology and the fact that phenotypical driver mutations like JAK2V617F are not exclusive to a particular MPN. The 2016 WHO 2016 classification [2]of MPNs include Chronic myeloid leukemia (CML), Chronic neutrophilic leukemia (CNL), Polycythemia vera (PV), Primary myelofibrosis (PM), Essential thrombocythemia (ET), Chronic eosinophilic leukemia (CEL) and MPN unclassifiable. WHO classification includes clinical, bone marrow morphology and molecular features to define disease entities and this multimodal approach forms the basis of diagnosis. These disorders are either BCR –ABL1 positive or negative. The BCR-ABL1 negative MNPs show positivity for JAK2 or CAL R OR MPL driver mutations.[3] A group of overlap disorders demonstrates features of both myeloproliferative and myelodysplasia and according to WHO 2016 includes Chronic myelomonocytic leukemia (CMML), Juvenile myelomonocytic leukemia (JMML), atypical chronic myelogenous leukemia, MDS/MPN with ringed sideroblasts and thrombocytosis and MDS/MPN unclassifiable.

**Objective**-Aim of this study is to provide practical approach , how to evaluate MPDs based on the clinical, histological and molecular genetic findings.

**Material and methods**-This was a retrospective study done in the department of pathology. We included cases of MPD which were diagnosed in our department based on the clinical details, laboratory features including the peripheral smear (PS) ,bone marrow aspirate (BMA) ,bone marrow biopsy and molecular genetic studies from January 2019 to January 2023. Record of patient's clinical details were taken. PS, BMA slides and bone marrow biopsy of all the cases were received in our department. PS and BMA smears were stained using Fields stain and were examined and findings were recorded. Biopsy of bone marrow was processed and stained using the Hematoxylin and eosin(H&E) stain and were studied according to the standard protocol. Findings of the PS, BMA and biopsy were evaluated and a diagnosis of MPD was made and were advised for further genetic studies. Based on the advice given on the Bone marrow reports, molecular genetics results were recorded.

**Inclusion criteria-**All cases of MPD diagnosed in our department. Exclusion criteria-Cases other than MPDs. Diluted marrow aspirates

## OBSERVATIONS AND RESULTS-

Out of total 22 cases ,16 cases were of CML with 14 cases in chronic phase and 02 cases in blast crisis.02 cases were of JMML, 01 case PV, one case CNL, one case CEL one case ET. CML cases showed BCR-ABL1 positivity while others were negative , CEL was positive for PDGFRA rearrangement while negative for PDGFRB gene rearrangement. In this study we found that MPNs are more common in male compare to female.

**Table 1 Age wise distribution of cases**

| Disease | Age (0-10) years | 11-20 years | 21-30 y years | 31-40 years | 41-50 years | 51-60 y years | 61-70 years | >70 years |
|---|---|---|---|---|---|---|---|---|
| CML | - | 03 | 04 | 04 | 02 | 01 | 02 | - |
| CNL | - | - | - | 01 | - | - | - | - |
| CEL | - | - | - | 01 | - | - | - | - |
| JMML | 01 | 01 | - | - | - | - | - | - |
| ET | - | - | - | - | - | - | - | 01 |
| PV | - | - | - | - | - | 01 | - | - |

**Table 2 Clinical presentation of various disorders**

| Disease | Clinical details |
|---|---|
| CML | Hepatosplenomegaly, abdominal pain, fatigue, fever, weight loss |
| CNL | Hepatosplenomegaly, fever, fatigue |
| CEL | Fever, bone pain, splenomegaly, joint pain |
| JMML | Splenomegaly, fever, lymphadenopathy, fatigue |
| ET | Bleeding from nose, multiple ecchymosis over body, hepatosplenomegaly |
| PV | Splenomegaly, fatigue, weight loss, headache, difficulty in vision. |

**Table 3 Laboratory findings of various disorders**

| Disease | Peripheral blood smear | Bone marrow | Others |
|---|---|---|---|
| CML | Marked Leukocytosis with immature granulocytes showing all stages. Basophilia, eosinophilia Thrombocytosis | Hypercellular marrow with marked myeloid hyperplasia showing all stages of maturation. Increased M:E Ratio Increased megakaryopoiesis with both hyper and hypolobate forms. | USG-Splenomegaly |
| CNL | Marked Leukocytosis with predominantly mature neutrophils and band forms and immature granulocytes <10 % and myeloblast 3% Polymorphs showing both right shift and left shift. | Hypercellular marrow with increased myelopoiesis with predominantly neutrophils and blast 3% and immature granulocytes <10 %. Increased M:E Ratio Increased megakaryopoiesis with both hyper and hypolobate forms. | Serum Uric acid-9.9 g/dl USG-Hepatospleno megaly |
| CEL | Leukocytosis with eosinophilia -48% along with mature neutrophils and immature granulocytes. | Hypercellular marrow with increased myelopoiesis and evidence of eosinophilia and eosinophilic precursors. | Serum Uric acid-9.5 g/dl USG-Hepatospleno megaly |
| ET | Leukocytosis Thrombocytosis with platelet count >1200000/cumm with giant platelets | Normocellular to hypercellular marrow with megakaryocytic hyperplasia showing hyperlobate forms. | Serum Uric acid-7.5 g/dl |
| PV | Normocytic normochromic blood picture with increased red cell count and hemoglobin 18 gm/dl and thrombocytosis | Panmyelosis with Erythroid hyperplasia with granulocytic and megakaryocytic proliferation. | Erythropoeitin-5.08mIU/ml USG-splenomegaly |
| JMML | Marked Leukocytosis with immature granulocytes showing all stages along with monocytosis. | Hypercellular marrow with increased myelopoiesis showing all stages of maturation along with monocytic proliferation with presence of monocytes and promonocytes. | USG-Hepatospleno megaly |

**Table 4 Molecular findings in various disorders**

| Disorder | Molecular genetic findings |
|---|---|
| CML | BCR-ABL Positive |
| CNL | BCR-ABL Negative, CSF3R mutation positive |
| CEL | BCR-ABL Positive<br>PDGFRA rearrangement positive |
| PV | BCR-ABL Negative, JAK2V617 F positive |
| ET | BCR-ABL Negative, JAK2 mutation positive |
| JMML | BCR-ABL Negative |

**Images:**

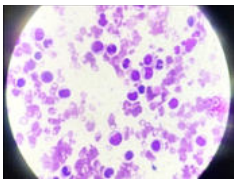

**Figure 1. CML - BMA smear showing all stages of maturation of granulocytic lineage.**

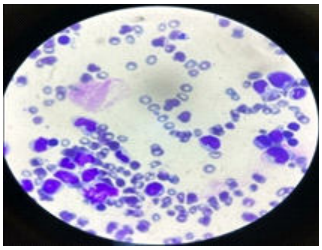

**Figure 2 JMML -BMA showing myelocytes and Monocytic proliferation**

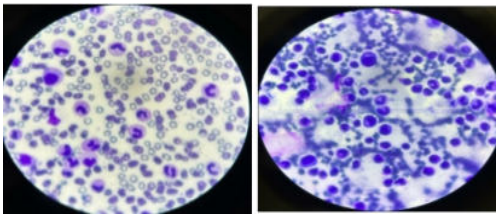

**Figure 3 CNL – a.)PS showing leucocytosis with neutrophilia. B)BMA smear showing predominantly Neutrophils and Band forms -CNL**

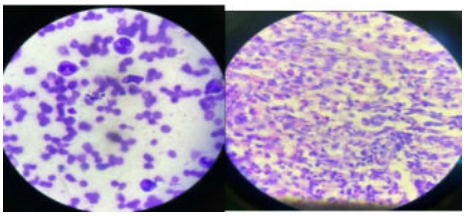

**Figure 4 Chronic eosinophilic leukemia- a) Peripheral smear b) Bone marrow biopsy showing eosinophilia**

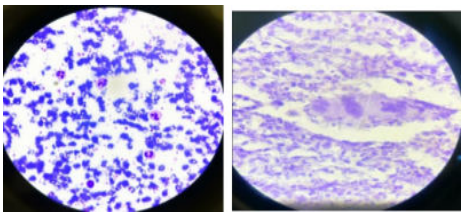

**Figure 5 a) PS showing thrombocytosis with giant platelets-ET b)Bone marrow biopsy showing megakaryopoiesis with mature hyperlobate forms - ET**

## DISCUSSION

Myeloproliferative neoplasms are a group of stem cell disorders characterized by overproduction of mature white cells, red cells or platelets. CML (4) is a clonal MPN arising from neoplastic transformation of pluripotent stem cell and is associated with BCR-ABL1 fusion gene located in the Philadelphia(Ph) chromosome (t 9:22) is the hall mark of CML (5).

In our study we found 16 cases of CML with 14 cases in chronic phase and 02 cases in blast crisis. A slight female preponderance was found with 09 cases in females and most of the cases were found in the age group of more than 40 years. The BCR-ABL1 fusion transcript was found to be positive. Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, et al. (2008) Mehta J, Wang H, Iqbal SU, Mesa R (2014) found that MPNs are more commonly seen in patients in their 60's or 70's [6,7]

CNL (8) is a BCR-ABL 1 negative neoplasm and a disorder of elderly .patients presents clinically with hepatosplenomegaly .PS shows leukocytosis with marked neutrophilia (>80%) and immature form less than 10% with blast <1%. Neutrophils may demonstrate toxic granules and normal to increased NAP score. Serum Uric acid levels is high. BM is hypercellular with mature granulocytosis and no dysgranulopoiesis with M:E ratio of >20:1 and myeloblast <5% .The

JAK 2V617F mutation is common in CNL and detection of CSF3R(colony stimulating factor 3 receptor gene) is one of the WHO diagnostic criteria for CNL. In our study we found one case of CNL with a male patient, age 35 years and presented with hepatosplenomegaly, fever and fatigue. Peripheral blood showed leukocytosis with persistent neutrophilia . Neutrophils and band forms constituted >80% with immature granulocytes <10% and myeloblast <3 %.serum uric acid was raised and bone marrow aspiration and biopsy showed hypercellular marrow with increased myelopoiesis with predominantly neutrophils and blast 3% and immature granulocytes <10 %.The BCR-ABL1 gene was found to be negative.

CEL is a clonal proliferation of eosinophilic precursors characterized by persistent peripheral blood eosinophilia > 1.5 x 109 ,with eosinophilic myelocytes, metamyelocytes and promyelocytes. In our study we found one case of CEL. Patient was a 32 year male presented with fever, bone pain, splenomegaly and joint pain. peripheral blood findings showed leukocytosis with neutrophilia and eosinophilia 48% with eosinophilic myelocytes and metamyelocytes. BM showed hypercellular marrow with increased myelopoiesis and evidence of eosinophilia and eosinophilic precursors. The genetic studies showed BCR –ABL1 gene negative and FISH on peripheral blood showed positive evidence of deletion of CHIC2 locus, resulting in fusion of FPI1L1 with PDGFRA in 90% cells. The PDGFRB and FGFR1 gene was found negative.

Patients with different subtype of MPNs may show distinct clinical and laboratory features, possibly related to the patient's gender and age (9,10)

ET (11) is a disease of elderly common in 50-60 years of age .It is a clonal myeloproliferative neoplasm characterized by marked megakaryocytic hyperplasia and thrombocytosis of more than 4.5 lacs /cumm along with platelet anisocytosis and presence of large platelets. JAK2 mutation is seen in 50-60% cases, CAL R in 20-25 % cases. WHO criteria includes thrombocytosis of more than 4.5 lacs /cumm. Bone marrow biopsy showing proliferation of megakaryocyte with increased number of large and mature megakaryocyte. Presence of JAK2, CALr or MPL mutation and not meeting criteria for BCR-ABL1 positive CML, PMF, PV or the myeloid neoplasms. We diagnosed one case of ET in our study. Patient was a 70 year /male, presented with complaints of Bleeding from nose, multiple ecchymosis over body and hepatosplenomegaly. Peripheral blood findings showed Leukocytosis and Thrombocytosis with platelet count >1200000/cumm with giant platelets. BM was normocellular to hypercellular marrow with megakaryocytic hyperplasia showing hyperlobate forms and it was BCR-ABL1 negative.

Polycythemia Vera (11) is also a BCR-ABL1 negative MPNs characterized by increased red cell mass, Increased blood volume, splenomegaly. There is panmyelosis . BM shows proliferation of all three lineages. It has three phases pre polycythemic, overt polycythemic and spent post polycythemic phase. According to WHO Major criteria for PV includes Hb >16.5g/dl in men and 16.0 g/dl in women. Or hematocrit >49% in men and 48 % in women or increased red cell mass >25% of mean. Bone marrow showing hypercellularity with panmyelosis and JAK 2V617F/exon 12 mutation. Almost all patients with PV harbor a JAK2 mutation (96% display the exon 14 JAK2V617F and 3% the exon 12 of JAK2 mutation).(12) We got one case of PV with complaints of splenomegaly, fatigue, weight loss, headache, difficulty in vision. Peripheral blood showed normocytic normochromic blood picture with increased red cell count and hemoglobin 18 gm/dl. and thrombocytosis. Bone marrow showed panmyelosis with Erythroid hyperplasia with granulocytic and megakaryocytic proliferation.

JMML is seen in young children characterized by granulocytic and monocytic proliferation. It is a clinically aggressive disease. Juvenile myelomonocytic leukemia is an aggressive pediatric myelodysplastic syndrome (MDS)/ myeloproliferative disorder (MPD) characterized by malignant transformation in the hematopoietic stem cell compartment with proliferation of differentiated progeny (13). JMML constitutes approximately 30% of childhood cases of myelodysplastic syndrome and 2% of leukemia. Fetal hemoglobin is increased and NAP score is elevated. in tour study we also found two cases of JMML, 02 Pediatric patients-01 year/male and 11 year/female patients presented with splenomegaly, fever, lymphadenopathy and fatigue. PS showed anemia, thrombocytopenia with marked leukocytosis with immature granulocytes showing all stages along with monocytosis. BMA showed hypercellular marrow with increased myelopoiesis showing all stages of maturation along with monocytic proliferation with presence of monocytes and promonocytes. Blast was less than 20 % BCR-ABL1 gene was found to be negative. The diagnosis of JML was made.

**CONCLUSION-** Evaluation of MPNs involve comprehensive hematological/laboratory workup comprising of Peripheral blood, bone marrow and cytogenetic analysis along with clinical findings. The WHO classification is based on all these parameters and help in diagnosis of MPNs. In this study we include clinical, bone marrow morphology and molecular features to define disease entities and this multimodal approach forms the basis of diagnosis.

**Conflict of Interest –** Nil

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