Clinicohematological study of spectrum of myeloproliferative neoplasms in a tertiary care hospital

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ABSTRACT
Myeloproliferative neoplasms (MPNs) are a group of disorders of hematopoietic stem cells which were initially recognised by William Dameshek in 1951. Objectives of the study were to diagnose and classify cases of myeloproliferative neoplasms according to 2016 revision of WHO classification of myeloid neoplasms and acute leukaemias, to study various haematological parameters of cases of MPNs (Peripheral smear findings, bone marrow aspirate and trephine biopsy) and their clinical manifestations, to record the cytogenetic/molecular genetic abnormalities of the cases and to categorise CML patients according to Hasford Risk Score as a predictor of prognosis. This study was a prospective study carried out in the Department of Pathology of a tertiary care hospital over two years from June 2016 to September 2018. The study included a total of 41 cases of MPNs. The cases of CMLs were diagnosed on peripheral blood findings, Bone marrow aspiration, Trephine biopsy Serum LDH and uric acid. CML was the most common MPN encountered (37/41; 90.24%) in the present study. Maximum serum LDH elevation was observed in CML cases with a mean value of 1396.6 U/L. Of the 37 CML cases, as per Hasford score, 17 cases were categorised into a low-risk group, 17 cases into an intermediate-risk group and 3 cases into a high-risk group. In the present study of Hasford score in CML cases, it was found that it helps in making a better-informed decision about the adaption of alternative high-risk treatment, and was of value in oncology practice.

INTRODUCTION
Myeloproliferative neoplasms (MPNs) are a group of disorders of hematopoietic stem cells which were initially recognised by William Dameshek in 1951. In 2016, the World Health Organization (WHO) revised the classification system of MPNs which includes chronic myeloid leukaemia (CML), BCR-ABL1-positive, chronic neutrophilic leukaemia (CNL), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocytosis (ET), chronic eosinophilic leukaemia, NOS (CEL, NOS) and myeloproliferative neoplasm, unclassifiable (MPN-U) (Jameel and Jamil, 2006). In India, CML is the most common leukaemia encountered (Srinivas et al., 2013).

This classification reflects a paradigm shift from the previous classification as genetic information is incorporated with morphological, cytochemical, immunophenotypic and clinical data into the diagnostic algorithms for myeloid neoplasm (Thiele et al., 1999).
The discovery of recently identified molecular mutations in MPNs now play an essential role as diagnostic as well as prognostic markers. As the philosophy of personalised “Tailor-made drug therapy” has come into the forefront, new drugs are being discovered to target these specific mutations. The study is an attempt to classify MPN cases according to the WHO 2016 Classification in correlation with BCR-ABL and JAK2 V617F mutation.

Chronic myeloid leukaemia has been a model disease for a variety of studies concerning scoring systems. The three principal risk scores, 1) Hasford 2) Sokal 3) European Treatment and Outcome Study (EUTOS) were established in different eras of CML therapy, with implication for disease outcome and prognosis. Hasford score in CML cases discriminates patients between high risk, intermediate-risk and low-risk groups and thus has an impact in predicting the disease outcome and prognosis. Thus, Hasford score helps physicians in making a better-informed decision about the adaption of alternative higher risk treatment options in cases diagnosed as CML.

**Aim**
To diagnose and classify cases of myeloproliferative neoplasms according to 2016 revision of WHO classification.

**Objectives**
1. To diagnose and classify cases of myeloproliferative neoplasms according to 2016 revision of WHO classification of myeloid tumours and acute leukaemias.
2. To study various haematological parameters of cases of MPNs (Peripheral smear findings, bone marrow aspirate and trephine biopsy) and their clinical manifestations.
3. To record the cytogenetic/molecular genetic abnormalities of the cases.
4. To categorise CML patients, according to Hasford Risk Score as a predictor of prognosis.

**MATERIALS AND METHODS**
This study was a prospective study carried out in the Department of Pathology of a tertiary care hospital over two years from June 2016 to September 2018. The study included a total of 41 cases of MPNs. A complete hemogram was done for patients presenting with weakness, pallor, fever, pain in the abdomen, abdominal distention and palpable hepatosplenomegaly. The cases of CMLs were diagnosed with peripheral blood findings. Bone marrow aspiration was performed for morphological evaluation to confirm the phase of the disease. Trephine biopsy was done in all the cases of MPNs. Serum LDH and uric acid values were noted in all cases. The Philadelphia-chromosome analysis was done for case diagnosed as CML by conventional cytogenetics and a baseline BCR: ABL ratio was recorded for the same. BCR-ABL1 transcript quantification was done by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). JAK2 mutation assay was done in peripheral blood by PCR for other subcategories of MPNs. All the 37 diagnosed CML cases were scored as per Hasford score and categorised into a low, intermediate and high-risk group. The patients diagnosed as CML were put on a standard dose of imatinib and followed up to September 2018. Haematological parameters, including a complete blood count and spleen size, were recorded every three months to assess response. A complete haematological response (CHR) was said to have been achieved if; Total white blood cell count < 10000/mm$^3$, Platelet count < 4.5 lakh /mm$^3$, No immature leucocytes in the peripheral blood No palpable splenomegaly, Early molecular response (EMR) was recorded using BCR: ABL1 (RT-PCR) percentage at the third month of therapy, after that major molecular response (MMR) and deep molecular response (DMR) was recorded up to September 2018.

**Inclusion criteria**
The MPN cases with cytogenetic/molecular studies as per the revised 2016 WHO criteria for classification for myeloproliferative neoplasms were included in the study

**Exclusion criteria**
The MPN cases without cytogenetic/molecular studies as per revised 2016 WHO classification for myeloproliferative neoplasms were excluded from the study.

**Statistical Analysis**
Data was recorded on a specially designed proforma. The results were compared between patients with different variables. The results were presented as rate, ratios, standard deviation, frequencies, percentages and positive predictive value in tables and figures.

**RESULTS AND DISCUSSION**
A total of 41 cases diagnosed as MPN on complete blood count, peripheral smear examination, bone marrow aspirate, bone marrow biopsy with cytogenetic JAK2 V617F mutations; and BCR-ABL1 mutation in cases of CML with molecular response data were studied. The study included a total of 41 cases.
Table 1: Distribution of MPN cases according to 2016 WHO classification of myelo proliferative neoplasms

| Diagnosis | Number of cases | Percentage |
|-----------|----------------|------------|
| CML       | 37             | 90.24      |
| PMF       | 01             | 02.44      |
| CNL       | 01             | 02.44      |
| PV        | 01             | 02.44      |
| MPN-U     | 01             | 02.44      |
| Total     | 41             | 100        |

Table 2: Mean value and standard deviation of hemoglobin, total leukocyte count, platelet count and hematocrit in MPN cases

| DIAGNOSIS | HEMOGLOBIN(g/dl) | TOTAL WBC COUNT (x 10^9/L) | TOTAL PLATELET COUNT (x 10^9/L) | HCT(%) |
|-----------|-----------------|--------------------------|-------------------------------|-------|
| CML       | 9.75 (+/-1.8)   | 153.35 (+/-105.2)         | 4.48 (+/-3.8)                 | 29.09 (+/-5.1)   |
| PMF       | 8.5             | 80.2                     | 1.75                          | 29.6 |
| CNL       | 10.9            | 81                       | 2.89                          | 37.8 |
| PV        | 20              | 13                       | 2.1                           | 60.2 |
| MPN-U     | 6.2             | 21.83                    | 2.32                          | 21 |

Table 3: Mean value and range of serum LDH and uric acid in MPN cases.

| Diagnosis | LDH (U/L) (Normal level: 313-618 U/L) | Uric acid(mg/dl) (Normal level: 3.5-8.5mg/dl) |
|-----------|--------------------------------------|---------------------------------|
| CML       | 1396.6                               | 5.59                            |
| PMF       | 1015                                 | 6.8                             |
| CNL       | 490                                  | 7.5                             |
| PV        | 550                                  | 7.2                             |
| MPN-U     | 400                                  | 4.7                             |

Table 1 finds that CML was the most common MPN encountered (37/41; 90.24%) in the present study. The most common presenting complaint in patients with CML was a weakness (23/37 cases, 62.16%), followed by fever (15/37 cases, 40.54%), pain in the abdomen (13/37 cases, 35.13%), and abdominal distention (13/37 cases, 35.13%). A single case of CNL presented with weakness, weight loss, pain in abdomen and difficulty in breathing. A single case of PV presented with plethora, weakness and pain in the abdomen. Weakness and pain in the abdomen were the presenting symptoms in a single case of MPN-U. The most common physical sign on examination of patients with a diagnosis of CML was splenomegaly (20/37 cases, 54.05%). Other physical symptoms noted were hepatomegaly (12/37 cases, 32.43%) and pallor (5/37 cases, 13.51%).

of MPNs, with 37 cases diagnosed as CML and one case each of PMF, CNL, PV and MPN-Unclassifiable.

CML, the most common MPN observed showed male predominance with male to female ratio of 1.5:1. Among the other subcategories of MPN, the cases of PMF, PV and MPN-U were seen in male patients, while the CNL was seen in a female patient. CML showed male preponderance with 22 out of 37 cases, i.e. 59.46%. The youngest patient was 13 years old, and the oldest patient was 75 years old. Mean age of patients diagnosed as CML in the present study was 50.4 years (+/-14.4 years). Maximum numbers of patients were seen in the 5th decade (17/37 cases, 45.94%). PMF, CNL and PV and MPN-U were observed in patients above 60 years of age group. A maximum number of cases of CML were found in the age group of 40 to 50 years (17/37, 45.94%).
Splenomegaly was the most typical sign in all the other subcategories of MPN.

**Section II: Hematological parameters**

Table 2 shows that the haematological parameters included in the study were haemoglobin, total leucocyte count, platelet count and hematocrit. Mean value and standard deviation of haemoglobin, total leucocyte count, platelet count and hematocrit.

**Peripheral smear**

Of the total 37 cases of CML, maximum cases (34/37 cases; 91.90%) presented in chronic phase (CML-CP), 2/37 cases (5.40%) in accelerated phase (CML-AP) and one case (2.70%) in blast crisis (CML-Blast crisis).

**Biochemical tests**

Table 3 reveals that the total serum LDH activity was elevated in all the cases of MPN. Maximum serum LDH elevation was observed in CML cases with a mean value of 1396.6 U/L. Serum uric acid levels were found to be reasonable in all cases of MPN.

**Results of cytogenetic analysis in cases of MPN**

All the cases of CML were BCR-ABL1 positive. Other subcategories of MPN as PMF and PV were JAK2 V617F mutation-positive. The MPN-U subcategory was JAK2 V617F positive and BCR-ABL1 negative. The CNL subcategory was BCR-ABL1 negative and was not studied for other mutations.

The above Table 4 finds that all the subcategories of MPN except primary myelo Fibrosis in overt fibrotic stage showed an increase in bone marrow cellularity and increased myelopoesis. Bone marrow aspirates and trephine biopsies in CML showed a hypercellular marrow with increased myelopoesis (100%), 24/37 cases (64.86%) showed a reduction in erythropoiesis, 13/37 cases (35.14%) showed normal erythropoiesis. 25/37 cases of CML (67.57%) showed average megakaryocyte population, and 11/37 cases (29.73%) showed an increase in megakaryocyte population. A single case of CML in blast crisis phase of CML showed decreased megakaryopoiesis (1/37 cases, 2.70%).

**Risk wise distribution of CML cases according to Hasford score**

Of the 37 CML cases, as per Hasford score, 17 cases were categorised into a low-risk group, 17 cases into an intermediate-risk group and 3 cases into a high-risk group at the first visit. All the patients in a low-risk group (17/17) achieved complete haematological response and early molecular response within three months. 16 out of 17 cases in the intermediate-risk group achieved complete haematological response and early molecular response within three months. In contrast, one case in the intermediate-risk group made the complete haematological response and early molecular response within six months. All the cases in low risk and intermediate-risk group achieved major molecular response (MMR)/ deep molecular response (DMR) in the time defined by European LeukemiaNet (ELN). Amongst the 3 cases in a high-risk group, two achieved complete haema-
tological response and early molecular response at six months and were then treated with second-generation tyrosine kinase inhibitors. One case in a high-risk group, diagnosed in CML-Blast crisis phase was deceased within a few days after diagnosis. Thus the Hasford score predicted prognosis accurately in 36 out of 37 cases, and the positive predictive value of the scoring system is 97.29%.

Recent discoveries in the molecular pathogenesis of each myeloproliferative neoplasm phenotype, with the new molecular diagnostic technology, has dramatically expanded the knowledge about these conditions and created a need for more streamlined diagnostic approach. The latest data indicates that the presence of various mutations carries significant prognostic value. Classification of patients according to their clinical, morphologic and cytogenetic features could also assist in selecting an appropriate therapeutic approach, that could lead to better treatment outcome. Although cellular and molecular studies in CML help improve the treatment and prognosis, today, Hasford Score / Sokal risk definition is required to plan the treatment strategy for CML patients.

Out of the total 41 cases diagnosed as MPN in a study period of 2 years, the incidence of BCR-ABL1 positive CML was 90.24% (37/41). The remaining four patients were BCR-ABL1 negative MPN, i.e. PMF one case, CML one case, PV one case and MPN-U one case.

**Chronic Myeloid Leukemia**

The age group in the range of 40 – 50 years was the most commonly affected by CML (17/37, 45.94%), with male predominance (22/37, 59.46%). The youngest patient was 13 years old, and the oldest patient was 75 years old. A study was done by [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) of 59 patients, 34 (58%) patients were male while 25 (42%) patients were females with an age range of 20 months to 70 years. The youngest patient was 13 years old, and the oldest patient was 75 years old. A study was done by [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) amongst the total 350 CML cases 245 (70%) patients were male, and 105 (30%) patients were females with 28% patients belonging to 41 to 50 years of age group. Thus, findings related to age and sex of CML cases in the present study are concordant with studies done by [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) and [Srinivas et al. (2013)](https://doi.org/10.13189/ijbct.2006.04.02.539-544). Weakness was the most common presenting symptom in the present study (23/37 cases; 62.16%), followed by fever (15 /37 cases; 40.54%), pain in the abdomen (13 / 37 cases; 35.13%) and abdominal distention (13/37 cases, 35.13%). The present study was in concordance with studies done by [Thiele et al. (1999)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) while fever (65%) was the commonest symptom in the study done by [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544).

**Clinical signs**

Splenomegaly (20 /37, 54.05%) was the most common sign in CML, followed by hepatomegaly (12/37, 32.43%) and whiteness (5/37, 13.51%). [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) found splenomegaly in 98% cases and hepatomegaly in 57% cases in their study of 59 cases of CML. In the research done by [Srinivas et al. (2013)](https://doi.org/10.13189/ijbct.2006.04.02.539-544), 70% of patients had splenomegaly, followed by pallor (38%) and hepatomegaly (20%). Bleeding (4%) and lymphadenopathy (3%) was seen rarely. Thus the findings related to clinical signs in the present study were comparable to studies done by [Jameel and Jamil (2006)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) and [Srinivas et al. (2013)](https://doi.org/10.13189/ijbct.2006.04.02.539-544).

In the present study in cases of CML mean value of Hb was 9.75gm/dl, mean WBC count was 153.35 x 10^9 /L and mean platelet count was 4.48 x 10^9 /L. Mean value of Hb and platelets were in concordance with studies done by [Hasford et al. (1998)](https://doi.org/10.13189/ijbct.2006.04.02.539-544) and [Bonifazi et al., 2000](https://doi.org/10.13189/ijbct.2006.04.02.539-544). Reported very high mean value of total WBC count. Our findings are in concordance with [Bonifazi et al. (2000)](https://doi.org/10.13189/ijbct.2006.04.02.539-544).

**Peripheral smear findings in CML**

Peripheral smears in cases of CML were normocytic normochromic (mean Hb /-1.8 g/dl), with marked leukocytosis (mean 153.35 +/-105.2 x 10^9/L) showing mature and immature leukocytes including metamyelocytes, myelocytes and promyelocytes; and absolute basophilia (mean basophil percentage 3.27%; range 0-25). The platelet count was normal in 18 out of 37 cases (48.65%), elevated in 16 out of 37 cases (43.24%) and reduced in three cases (8.11%). Of the three cases with reduced platelet count, two presented in the accelerated phase of CML and one in blast crisis phase of CML. These findings were comparable to the study done by [Thompson et al. (2015)](https://doi.org/10.13189/ijbct.2006.04.02.539-544).

**Biochemical results**

Mean value of serum LDH and serum uric acid in patients diagnosed as CML was found to be 1396.6 U/L and 5.59 mg/dl, respectively. In the present study, LDH was raised in all the 37 cases (100%) of CML (Normal range:313 – 618 U/I). Serum LDH values were higher in CML. This is attributed to the disintegration of an increased number of leucocytes. Serum uric acid levels were found to be normal in all the cases of CML (Normal range: 3.5 – 8.5 mg/dl).

**Bone marrow findings in CML**

In the present study, bone marrow cellularity was increased in all 37(100%) cases of CML. Myelopoiesis was increased in all the cases (37/37, 100%). Erythropoiesis was found to be suppressed
in 24/37 (64.86%) cases, whereas it was normal in 13 out of 37 (35.14%) cases. Megakaryocyte number was normal in 25 / 37 (67.57%) cases, increased in 11 / 37 (29.73%) cases and reduced in 1/37 (2.70%) case of CML in blast crisis phase of CML. These findings were in concordance with studies done by Khonglah et al. (2002) and Tatapudi and Basu (2005).

**Hasford score as a predictor and actual response in CML**

Thus, the Hasford score predicted prognosis accurately in 36 out of 37 cases, and the positive predictive value of the scoring system is 97.29%. The results of the present study were in concordance with the results of the research done by Telen et al. (2018) and Dybko et al. (2016).

**Primary myelofibrosis**

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm, characterised by a predominant proliferation of abnormal megakaryocytes and granulocytes in the bone marrow and is associated with reactive deposition of fibrous connective tissue and with extramedullary haematopoiesis in fully developed disease.

There is a stepwise evolution of the disease from an initial prefibrotic or early stage, characterised by hypercellular bone marrow with minimal or absent reticulin fibrosis, to an overt fibrotic stage with marked reticulin or collagen fibrosis in the bone marrow and osteosclerosis. The fibrotic stage of PMF is clinically characterised by leukoerythroblastosis in the peripheral smear, with teardrop-shaped red blood cells, hepatomegaly, and splenomegaly (Andreasson et al., 2005). We encountered only one case of primary myelofibrosis which was in the overt fibrotic stage and was diagnosed in a 72 years old male patient.

We observed a higher total leukocyte count compared to other studies and lower platelet count and haemoglobin. This finding was similar to the results by Rojer et al. (1978) and Simonovic et al. (2007). The case fulfilled all the three significant criteria and all five minor criteria of the revised 2016 WHO criteria of primary myelofibrosis, in an overt fibrotic stage. A study by Michiels (1999), reported the presence of atypical, enlarged and immature megakaryocytes with a predominance of a cloud of nuclei in idiopathic myelofibrosis. In a study by Rudzki et al. (2006), he stated that megakaryocytes in myelofibrosis are larger than normal and showed markedly greater size variability. Thus the findings related to bone marrow biopsy features were comparable to studies done by Michiels (1999) and Rudzki et al. (2006).

**Chronic Neutrophilic Leukemia**

Chronic Neutrophilic Leukemia (CNL) is a rare myeloproliferative neoplasm, now known to be pathogenetically associated with oncogenic mutations in the gene for the colony-stimulating factor 3 receptor (CSF3R). According to WHO 2016, more than 200 cases of CNL have been reported with only 150 of them have met the current diagnostic criteria. We encountered one case of CNL, a 72-year-old female. In studies done by Meggendorfer et al. (2014) the mean age of presentation was 73 years (31-80), and by Elliott et al. (2005) the mean age of presentation was 67 years (26-80). The patient presented with fatigue, weight loss, bruise, pain in abdomen and difficulty in breathing. These findings were similar to studies done by Zittoun et al. (1994) and Hasle et al. (1996). Abdominal distension and hepatosplenomegaly were noted. CT Thorax findings were diffuse ground-glass opacities diffusely involving the bilateral lung fields with fibrotic changes and consolidation, left ventricular hypertrophy and multiple lymph nodes in the paraaortic and paratracheal region. In a study done by You and Weisbrot (1979), hepatosplenomegaly was the most constant presenting feature reported, whereas gout and pruritis were the other possible features noted. The most frequent finding was hepatosplenomegaly while lymphadenopathy was uncommon finding in a study done by Menezes and Cigudosa (2015). Thus the findings related to patient symptoms were comparable with studies done by You and Weisbrot (1979). Bone marrow biopsy showed a hypercellular marrow for age with cellularity of 80%, predominant myeloid series of neutrophilic type, no foci of fibrosis with no evidence of abnormal megakaryocytes and granulomas. The case was reported as Neutrophilic myeloid hyperplasia, consistent with CNL. The case fulfilled 2016 WHO criteria for CNL including peripheral smear and bone marrow criteria, with BCR-ABL1 negative cytogenetic and no evidence of PMF, PV, ET or plasma cell neoplasia, with persistent neutrophilia and no identifiable cause of reactive neutrophilia. Similar findings were reported by Menezes and Cigudosa (2015).

**Polycythemia Vera**

Polycythemia Vera is a myeloproliferative neoplasm characterised by absolute erythrocytosis not driven by erythropoietin (Epo). We encountered one case of PV, a 70-year-old male. In a study by Tang et al. (2017) the median age at diagnosis was 54 years (range, 11–84 years) and the male to female ratio was 1.2:1. The patient presented with plethora, weakness and pain in the abdomen. On USG,
splenomegaly was noticed. These findings were comparable to studies done by Michiels et al. (2006). In the present study, the values of Hb, HCT and WBC count were comparable to study done by Khonglah et al. (2002), while the platelet count was lower compared to the studies mentioned above. LDH and uric acid were found to be 550 U/L and 7.2 mg/dl, respectively. A similar finding was observed in a study done by Andreasson et al. (2005). Serum erythropoietin level was within normal limits. Peripheral smear, in case of PV, showed a normocytic normochromic picture with mild leukocytosis (WBC count 13 x 10^9/L). Similar findings were reported in studies done by Marchioli et al. (2005) and Knoops et al. (2008).

**Myeloproliferative neoplasm – Unclassifiable**

The designation of MPN-U is applied to cases with clinical, morphological, laboratory and molecular features of MPN but fail to meet the diagnostic criteria for any of the specific MPNs. Cases that present with features that overlap between two or more of the MPN categories are also included in the MPN-U category. Many cases belonging to MPN-U are in a very early stage of the disease and differentiating between ET, profibrotic stage of PMF and pre-polycythemic phase of PV is difficult. There was one case of MPN-U, a 67 year male in the present study. In a review by Iurlo et al. (2017), the median age of presentation was 61 years with female preponderance. The patient of MPN-U presented in the year 2016 with weakness, pallor, pain in the abdomen and abdominal distention. Clinical examination and USG findings showed hepatosplenomegaly. These findings were comparable to the study done by Iurlo et al. (2017) where splenomegaly was the most common symptom (31/71 cases, 43.7%).

Laboratory findings in a case of MPN-U were Hb-6.2 g/dl, HCT-21%, WBC count-21.83 x 10^9/L and platelet count-232 x 10^9/L. The findings in the present study were lower compared to the study done by Alessandra et al (2017). The value of LDH and uric acid levels were 400 U/L and 4.7 mg/dl. This finding was comparable to the study done by Iurlo et al. (2017) where the median LDH value was 353 U/L (127-839).

Peripheral smear in case of MPN-U showed a microcytic hypochromic picture with teardrop cells, leukocytosis with neutrophilia and shift to the left up to blast (1%) of myeloid series, platelets were adequate (216000/cumm) in number. Philadelphia chromosome was negative, and JAK2 V617F was positive. BMA, in case of MPN-U, showed a hypercellular marrow, with markedly increased myelopoiesis and normal maturation. Erythroid series showed normoblasts erythropoiesis, with M:E ratio of 5:1 and 2% blast population. BM aspiration findings were suggestive of chronic myeloproliferative disorder. BM trephine biopsy sections displayed fibrosis (Grade I) with panmyelosialysis and marked increase in myeloid and erythroid cells. Megakaryocytes were increased in number, clustered, and some of them showed dysmorphic features. The megakaryocyte proliferation with morphological abnormalities were the features more in favour of profibrotic phase of PMF. Bone marrow findings showed features overlapping profibrotic phase of PMF and polycythemia vera.

The patient was put on hydroxyurea, and he responded well. In 2018 he was admitted with complaint of giddiness and pain in the abdomen. On PS there was leukocytosis with a shift to the left up to blast > 20%. According to WHO, Blast > 20% on PS or BM in a case of MPN-U, indicates blast phase (i.e. acute leukaemia transformation) of previously diagnosed MPN-U. The present study had a small sample size of 41 cases, in which CML formed the major group, i.e. 37/41 cases and PMF, CNL, PV and MPN-U were having representation with an only single example each. While there were no cases of disease entity listed in WHO 2016 classification of MPN, such as ET and CEL-NOS. Hence comparison with other studies due to a limited number of cases was difficult.

**CONCLUSION**

Clinical and haematological findings along with characteristic cytogenetic mutation according to 2016 WHO classification of Myeloproliferative neoplasms, can help arrive at the correct diagnosis of MPNs. BCR-ABL1 and JAK2 mutation studies help in diagnosis and initiating appropriate treatment strategies for these patients. In the new era of ‘tailor-made treatment’ and ‘targeted therapy’ the use of cytogenetic mutations to characterise the disease prognosis and outcome, justifies the approach of the revised 2016 WHO classification. These mutation analyses give us a complete insight into the biology of the disease, thus defining the real disease entity. Though these are relatively high-cost tests, these have added advantage of being accurate, reproducible and add valuable information to morphology in the classification of diseases. In the present study of Hasford score in CML cases, it was found that it helps in making a better-informed decision about the adaption of alternative high-risk treatment, and was of value in oncology practice.
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Conflicts of interest

We all the authors declare no conflict of interest.

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