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Original Article

Pathology Section

Importance of Histological Pattern Recognition in Diagnosing Myeloproliferative Neoplasms in the Molecular Era: A Cross-sectional Study

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ABSTRACT

Introduction: Even after the inclusion of bone marrow features as major criterion in specific diagnosis of Myeloproliferative Neoplasms (MPNs), it is not given satisfactory importance in laboratory practice due to several reasons. Since bone marrow biopsy and histopathological examination is a simple procedure, proving its diagnostic utility in MPNs can be useful especially in resource-poor settings.

Aim: To identify the importance and reproducibility of the histological pattern recognition in diagnosing MPNs within a blinded clinical scenario.

Materials and Methods: This was a two-year cross-sectional analytical study done in the Department of Pathology at Guntur Medical College, Guntur, Andhra Pradesh, India from June 2021 to May 2023. Bone marrow biopsies from cases that were diagnosed as MPNs using a multidisciplinary comprehensive approach were included in the study. All the bone marrow biopsies were reviewed and re-evaluated by three experienced pathologists independently. The reviewers were blinded to clinical, laboratory and molecular data, excepting age and gender. Each pathologist gave an independent histological diagnosis based on his/her observations. Comprehensive multidisciplinary diagnosis was considered the gold standard to calculate diagnostic accuracy, sensitivity, specificity and degree of consensus of bone marrow histology. Data was analysed for kappa value to identify degree of agreement in all parameters between the different pathologists using Statistical Package for the Social Sciences (SPSS) software version 24.0.

Results: A total of 47 cases of MPNs were included in the present. Highest diagnostic accuracy, specificity and sensitivity of bone marrow histology was obtained in Overt Myelofibrosis (OMF) (100%, 100%, and 100%, respectively), followed by Chronic Myeloid Leukaemia (CML) (80%, 85.7%, and 97%, respectively). Of all the morphological features tested for reproducibility, highest interobserver agreement was found in cellularity (kappa coefficient of 0.83), megakaryocytic hyperplasia (kappa coefficient of 0.88), and osteosclerosis (kappa coefficient of 0.82).

Conclusion: There is a moderate level of agreement and reproducibility between different histological parameters and good accuracy, sensitivity and specificity of bone marrow histopathology in identifying various MPNs. This can be very useful in resource-poor settings and in the early stages of disease evolution.

Keywords: Erythroid, Fibrosis, Megakaryocyte morphology, Myeloid

INTRODUCTION

Since times unknown, morphology (gross and microscopic) has remained the modus operandi in diagnosing diseases in modern medicine. However, with the advent of newer ancillary techniques and diagnostic methods, morphology is now becoming an elapsed art in diagnostic pathology. The MPNs are one such group of disorders where genetic testing has become the most common and obvious investigation of choice, relegating bone marrow morphology to the background [1].

Even after the inclusion of bone marrow features as major criterion in specific diagnosis of MPNs [2], it is not given satisfactory importance in laboratory practice due to several reasons. Early stages of Polycythaemia Vera (PV), essential thrombocythaemia and primary myelofibrosis share similar histological features and hence can be difficult to differentiate [3]. The present study was taken up to identify the usefulness of the histological pattern recognition in diagnosing MPNs within a blinded clinical scenario and to identify the reproducibility of various diagnostic features enlisted in the WHO 2022 classification [2], and to determine the relative significance of each individual features.

The objectives of the present study was to explore the relative relevance of diverse histopathological diagnostic features enlisted by the WHO 2022 in diagnosing MPNs, to find the sensitivity, specificity and correlation between the histopathological diagnosis and molecular genetics of various MPNs and to establish the reproducibility of various histopathological diagnostic features among different pathologists in coming to a diagnosis of MPNs. This study aimed to identify the effectiveness of bone marrow morphology in diagnosing MPNs.

MATERIALS AND METHODS

The present study was a two-year retrospective cross-sectional analytical study performed in the Department of Pathology of Guntur Medical College, Guntur, Andhra Pradesh, India between June 2021 and May 2023. All procedures performed in the current study were approved by the Institutional Review Board (IRB) and Institutional Ethics Committee (IEC), in accordance with the 1963 Helsinki declaration and its later amendments (Certificate Number: GMC/002/2023).

Inclusion criteria: A total of 47 established cases of MPNs, identified using an interdisciplinary approach (clinical, pathological and molecular via Real-time Polymerase Chain Reaction), cases that met the adequacy criteria for bone marrow biopsy (minimum length of 1.5 cm, non tangential biopsies with a minimum of 6-8 intertrabecular spaces) were included in the study.

Exclusion criteria: Inadequate biopsies and cases with incomplete clinical and molecular data were excluded from the study.

Study Procedure

All specimens were routinely fixed in 10% buffered formalin, decalcified using 2% EDTA solution and subsequently processed. Paraffin-embedded tissue blocks were sectioned and stained with

haematoxylin and eosin, and reticulin stains. All the 47 biopsies were reviewed and re-evaluated by three experienced pathologists. The reviewers were blinded to clinical, laboratory and molecular data, with the excepting age and gender. Each pathologist evaluated the samples using a systematic approach and recorded his observations in total of nine major parameters. Each pathologist gave an independent histological diagnosis (CML, PV, Essential Thrombocythemia (ET), Prefibrotic Myelofibrosis (PMF), or Overt Myelofibrosis (OMF)) based on their observations. Megakaryocyte morphology was analysed using the morphological definitions as enlisted in the study by Koopmans SM et al., [3]. In this study, a case was considered to be correctly diagnosed histologically when at a minimum two out of the three pathologists independently provided the same diagnosis as the final comprehensive diagnosis.

Furthermore, the study analysis of the reported incidence of individual morphologic features in different MPNs was performed to understand their relative importance for diagnosis. Morphologic features that were present in more than 80% of cases were considered as plausibly important for diagnosing MPNs.

STATISTICAL ANALYSIS

All the data were tabulated using Microsoft Excel 2020. A comprehensive multidisciplinary diagnosis was taken as the reference diagnosis to calculate diagnostic accuracy, sensitivity, specificity and degree of consensus. Data were analysed for Kappa value [4] to identify degree of agreement in all parameters between the different pathologists, using SPSS software version 24.0.

RESULTS

A total of 47 cases of MPN were included in the study. The final comprehensive diagnosis and molecular status of all the cases are shown in the [Table/Fig-1]. The importance of histopathological pattern recognition in diagnosing MPNs was assessed by calculating accuracy, sensitivity, and specificity of histopathological features alone in diagnosing MPNs.

S. No.	Diagnosis	Number of cases	Molecular data			
			BCR-ABL	JAK2V617F	CALR	MPL
1	Chronic Myeloid Leukaemia (CML)	14	14	-	-	-
2	Polycythemia Vera (PV)	19	-	19	-	-
3	Essential thrombocythemia	6	-	4	2	-
4	Prefibrotic Myelofibrosis (PMF)	5	-	3	2	-
5	Overt myelofibrosis	3	-	1	1	1
	Total	47	14	27	5	1

[Table/Fig-1]: Comprehensive clinical diagnosis along with molecular data.

Diagnostic accuracy of bone marrow histology: The diagnostic accuracy, sensitivity and specificity of the bone marrow histological diagnosis in present study is tabulated in [Table/Fig-2]. Of the 14 cases of CML, 12 were accurately diagnosed as CML by at least two of the three pathologists, while the remaining two cases were diagnosed as PV. Of the 19 cases of PV, 12 cases were correctly classified under PV; of the remaining seven cases, three were placed under PMF, and one as CML. Of the six cases of ET, five were accurately diagnosed, and one was placed under PMF. Of the five cases of PMF, three were accurately diagnosed and the remaining two cases were diagnosed as PV. All the three cases of Overt Myelofibrosis were correctly placed as MF by all the three pathologists.

Relative relevance of morphological features in establishing diagnosis: As illustrated in the [Table/Fig-3-8], in CML, hypercellularity with increased granulopoiesis and left shift were the most important feature that helped in arriving at a diagnosis in almost all cases. The next most useful features included presence of small-sized, hypolobated (dwarf) megakaryocytes. In PV, hypercellularity with panmyelosis, presence of small and medium-sized megakaryocytes, and small and loose cluster formation were considered useful. In PMF, hypercellularity with increased granulopoiesis and megakaryopoiesis, presence of large megakaryocytes in loose clusters exhibiting hypolobulations and hyperlobulation, were found to be most useful. In ET, increased megakaryopoiesis with presence of large hyperlobated megakaryocytes in loose clusters were noted as useful features. In Overt Myelofibrosis, presence of large megakaryocytes, hyperlobated nuclei, maturation defects, naked nuclei, endosteal translocation and increased reticulin were identified as the most useful features in distinguishing these cases from other MPNs.

Histopathological features of bone marrow biopsies and molecular status in ET and PMF: In the present study, a total of 11 cases of ET and PMF were included. As depicted in the [Table/Fig-9], of the 11 cases, seven cases had JAK2V61 7F mutation, and four cases had CALR mutation by real-time polymerase chain reaction. It was found that presence of reticulin fibrosis, dense clusters of megakaryocytes, maturation defects and naked nuclei were more common in patients with the CALR mutation.

Histological assessment and reproducibility: The degree of agreement among the three pathologists for different histopathological parameters was calculated using consensus diagnosis as the standard. Of all the parameters, there was excellent agreement in evaluation of hyperplasia of megakaryocytes, osteosclerosis, and cellularity. Other parameters showed fair to good degree of agreement, as shown in the [Table/Fig-10].

Despite the differences on agreement of different variables, the pathologists could accurately diagnose 35 cases out of the total 47 cases with histomorphological features alone (74.5% of all cases).

DISCUSSION

The notion of myeloproliferative disorders was initially proposed by Dameshek in 1957 to describe a group of conditions characterised by overproduction of mature blood cells [5]. Over time, this concept underwent evolution and metamorphosis, leading to the present WHO classification of MPNs, which is based on an interdisciplinary approach [2]. MPNs are broadly classified as BCR-ABL positive CMLs and BCR-ABL negative (Philadelphia negative) MPNs, which include PV, ET, PMF, and MF [6].

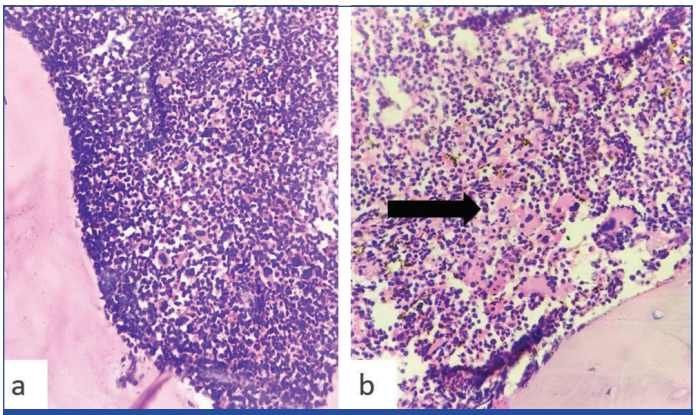
Despite being categorised as distinct entities the PV, ET, PMF, and MF exhibit a considerable degree of pathogenetic, morphological and clinical overlap. This intertwine provides these entities with the potential to transform into one another and progress into aggressive diseases, like fibrosis and blastic transformation. Aforesaid, since

S. No.	Comprehensive diagnosis	Total number of cases	Number of cases that were histologically diagnosed	False positives	False negatives	Accuracy	Sensitivity	Specificity
1.	Chronic Myeloid Leukaemia (CML)	14	12	1	2	80%	85.7%	97%
2	Polycythemia Vera (PV)	19	12	4	7	52.1%	63.1%	87.5%
3	Essential thrombocythemia	6	5	3	1	55.5%	83.3%	93.1%
4	Prefibrotic Myelofibrosis (PMF)	5	3	4	2	33.3%	60%	91.3%
5	Overt myelofibrosis	3	3	-	-	100%	100%	100%

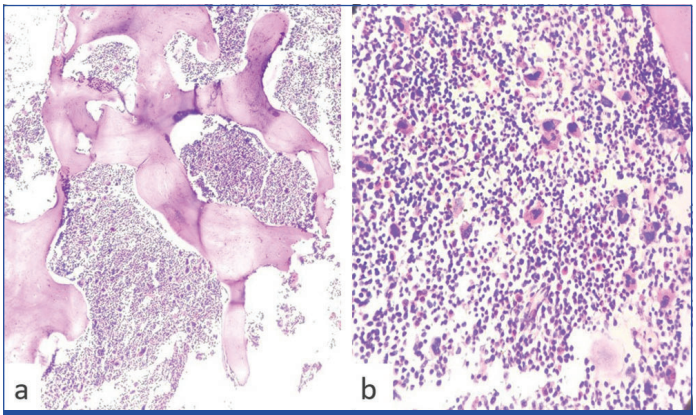
[Table/Fig-2]: Table depicting accuracy, sensitivity, specificity of histopathological diagnosis in MPNs.

Bone marrow morphology features		CML	PV	PMF	ET	OMF
Cellularity	Age related increase	100	100	100	16.6	66.6
Granulopoiesis	Increase in quantity	100	94.7	100	0	66.6
	Left shifted	100	31.5	60	0	66.6
Erythropoiesis	Increase in quantity	14.2	84.2	20	0	0
	Left shifted	0	21	20	0	0
Megakaryopoiesis	Increased in quantity	57.1	94.7	100	83.3	66.6
Size of cells	Small	100	84.2	40	50	33.3
	Medium	42.8	84.2	60	83.3	66.6
	Large	21.4	63.1	100	66.6	100
	Giant	0	21	60	66.6	66.6
Histotopography	Endosteal translocation	0	5.2	60	33.3	100
Cluster formation	Small clusters (>3 cells)	50	89.4	60	66.6	33.3
	Large clusters (>7 cells)	14.2	15.7	0	33.3	33.3
	Dense clusters	0	5.2	0	16.6	66.6
	Loose clusters	8.5	84.2	100	83.3	33.3
Nuclear features	Hypolobulation (bulbous)	85.7	52.6	80	66.6	33.3
	Hyperlobulation (staghorn-like)	7.1	78.9	80	100	100
	Maturation defects	7.1	5.2	40	33.3	100
	Naked nuclei	0	0	60	33.3	100
Fibrosis	Increased reticulin	7.1	10.5	60	33.3	100
	Increased collagen	0	0	0	0	66.6
	Osteosclerosis	0	0	0	0	66.6

[Table/Fig-3]: Relative incidence of histopathological discriminating features in the present study.

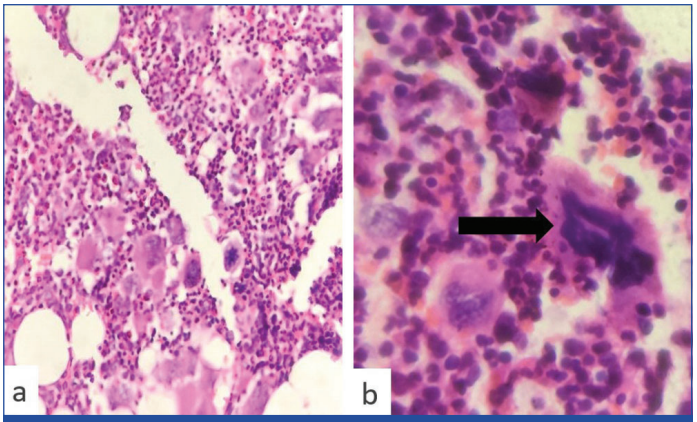


[Table/Fig-4]: Chronic Myeloid Leukaemia (CML): Hypercellular marrow with increased left shifted granulopoiesis with presence of dwarf megakaryocytes (arrow) (H&E, a-4x,b-40x).

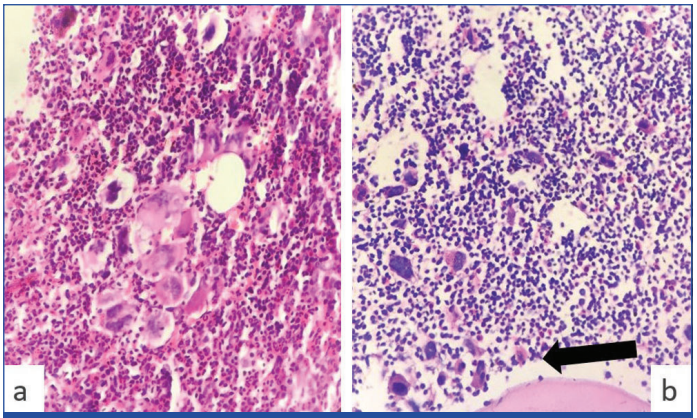


[Table/Fig-5]: Polycythemia Vera (PV)- Hypercellular marrow with panmyelosis and polymorphic megakaryocytes in small, loose clusters and scattered individually (H&E, a-4x,b-40x).

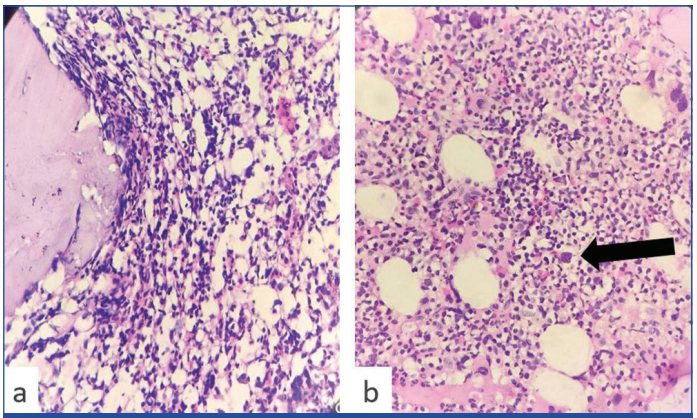
the treatment protocols (novel targeted agents) and prognosis differ significantly among these entities, it is crucial to identify the features that aid in discerning them apart from each other [7,8]. The present



[Table/Fig-6]: Essential Thrombocythemia (ET)- Normocellular marrow with large and loose clusters of megakaryocytes with plenty of hyperlobulated forms (arrow) (H&E, a-10x,b-100x).



[Table/Fig-7]: Prefibrotic Myelofibrosis (PMF) - Hypercellular marrow with increased granulopoiesis, large and dense clusters of megakaryocytes showing maturation defects, naked nuclei and endosteal translocation (arrow) (H&E, a-10x,b-10x).



[Table/Fig-8]: Overt Myelofibrosis- Normocellular to hypocellular marrow with increased reticulin and collagen deposition and naked megakaryocytes (arrow) (H&E, a-10x,b-10x).

Bone marr ow morphology features		JAK2V617F (n=7)		CALR (n=4)	
		Number	%	Number	%
Cellularity	Age related increase	4	57.1	2	50
Granulopoiesis	Increase in quantity	3	42.9	2	50
	Left shifted	2	28.5	1	25
Erythropoiesis	Increase in quantity	1	14.2	0	0
	Left shifted	1	14.2	0	0
Megakaryopoiesis	Increased in quantity	7	100	4	100
Size of cells	Small	5	71.4	1	25
	Medium	5	71.4	3	75
	Large	7	100	3	75
	Giant	4	57.1	3	75
Histotopography	Endosteal translocation	4	57.1	1	25

Cluster formation	Small clusters (>3 cells)	4	57.1	3	75
	Large clusters (>7 cells)	2	28.5	1	25
	Dense clusters	0	0	1	25
	Loose clusters	6	85.7	4	100
Nuclear features	Hypolobulation (bulbous)	5	71.4	3	75
	Hyperlobulation (staghorn-like)	6	85.7	4	100
	Maturation defects	2	28.5	3	75
	Naked nuclei	1	14.2	3	75
Fibrosis	Increased reticulin	1	14.2	3	75
	Increased collagen	0	0	0	0
	Osteosclerosis	0	0	0	0

[Table/Fig-9]: Histopathological characteristics with respect to JAK2V617F (7 cases) and CALR (4 cases) mutational status.

Interobserver agreement	Kappa coefficient	Bone marrow biopsy morphological features
Strong	0.88	Megakaryocytic hyperplasia
	0.83	Bone marrow cellularity
	0.82	Osteosclerosis
Moderate	0.67	Endosteal translocation of megakaryocytes
Weak	0.43	Myeloid hyperplasia
	0.42	Grading of fibrosis
	0.41	Left shifted granulopoiesis
	0.41	Erythroid hyperplasia
	0.41	Megakaryocyte cluster formation
Minimal	0.33	Megakaryocyte size
	0.30	Left shifted erythropoiesis
	0.21	Nuclear abnormalities in megakaryocytes

[Table/Fig-10]: Interobserver agreement in assessment of the histopathological features of bone marrow biopsies in the present study.

study was taken up in this light to emphasise, compare and correlate bone marrow biopsy morphological features in different MPNs.

Even in this molecular era, bone marrow evaluation remains the mainstay of diagnosis, classification and prognostication in MPNs [7], and this is highlighted by the WHO by including it as a major criterion in diagnosis of all MPNs [2]. However, there are very few studies which have evaluated the diagnostic accuracy in utilising bone marrow histology alone in MPNs [9]. This paucity of literature about diagnostic accuracy, sensitivity and specificity of bone marrow histology alone in comparison with MPN diagnosis using an interdisciplinary approach as gold standard is noteworthy. In the present study, it was found that 74.5% of cases were accurately diagnosed using bone marrow histology alone, with no peripheral blood counts, clinical data or molecular knowledge. This finding underlines the importance of performing bone marrow aspiration and biopsy in all suspected cases of MPNs, especially in resource-poor setting or settings where molecular testing is still not available. Further, it was found that bone marrow histology had very high specificity and hence may help to distinguish neoplastic from reactive cases [7]. Although the sensitivity observed in this study appears limited, it can be enhanced even more in real-life scenarios by leveraging access to peripheral blood counts and clinical data. Present study results are in concordance with those obtained by Alvarez-Larran A et al., [Table/Fig-11] [9].

Yet, as evidenced in the present study and pointed out by various authors [5-11], there is no single morphological feature that is pathognomonic for diagnosis; rather, it is histological pattern recognition that can help in diagnosing these entities distinctly. In the present study, the most critical features that were useful for arriving at a diagnosis where overall bone marrow cellularity (age-adjusted), megakaryocytic morphology, localisation and fibrosis.

Diagnosis	Present study, (2025)		Alvarez-Larran A et al., [9] study (2014, Barcelona, Spain)	
	Sensitivity	Specificity	Sensitivity	Specificity
CML	85.7%	97%	-	-
PV	63.1%	87.5%	32.5%	100%
ET	83.3%	93.1%	54%	98.5%
PMF	60%	91.3%	79%	92%
MF	100%	100%	75%	98%

[Table/Fig-11]: Comparative analysis of sensitivity and specificity [9].
*CML: Chronic myeloid leukaemia; PV: Polycythemia vera; ET: Essential thrombocythemia; PMF: Prefibrotic myelofibrosis; and OMF: Overt myelofibrosis

Present study findings associates with various other authors [7-9]. In CML, hypercellularity with left-shifted granulopoiesis and dwarf megakaryocytes were most useful features for arriving at a diagnosis. In PV, hypercellularity with panmyelosis, which was most prominent in the subcortical marrow spaces, along with presence of pleomorphic megakaryocytes in loose and small clusters was the most common histological pattern. In ET, the most common histological patterns were presence of lone megakaryocytic hyperplasia, presenting large megakaryocytes with hyperlobated nuclei. Hypercellularity, reticulin fibrosis, endosteal translocation and dense clustering of megakaryocytes were features that were useful in differentiating ET and PMF. In myelofibrosis, all the cases showed prominent maturation defects and naked nuclei of megakaryocytes, along with endosteal translocation and obvious fibrosis. Present study findings and relative incidence of each histological parameter are in concordance with several studies [12-15].

In the present study, histopathology was analysed in correlation with mutational status in the 11 cases of ET and PMF. It was found that reticulin fibrosis, dense clustering of megakaryocytes, maturation defects, and naked nuclei were more common in CALR-mutated cases comparison with JAK2V617F-mutated cases. Various study have compared genetic mutations with clinical features and suggested that CALR-mutated cases were more common in younger group and are associated with higher platelet counts, lower erythrocyte counts, leukocyte counts, haemoglobin and haematocrit, as well as an increased risk of progression to myelofibrosis [16,17].

In the present study, all the 19 cases of PV included showed JAK2V617F mutation only. Studies have revealed that approximately 3% of PV has a functionally similar mutation in JAK2 exon 12 and not JAK2V617F mutation. Scott LM et al., in their study showed that patients with this mutation exhibit prominent erythroid hyperplasia with reversal of M:E ratio, very mild megakaryocytic atypia, and minimal clustering, as opposed to patients with PV due to JAK2V617F mutation [18]. Thus, studies show that there is a good genotype-phenotype correlation and bone marrow histopathology can provide insight into this relationship [7,9,16-18].

Many authors opine that while the WHO has placed significant emphasis on trephine biopsies, there is potential for improved diagnostic accuracy and reproducibility by jointly examining aspirate and biopsy slides [6,7,18]. Brousseau M et al., also proposed the performance of bone marrow biopsies biennially in all cases of MPNs to ascertain morphological changes over time for disease surveillance and prognostication [19].

Numerous studies have reported conflicting results regarding the reproducibility of the WHO classification of MPNs based on morphological criteria [3,6,10,11,19,20]. In the present study, lowest degree of agreement was identified in quantification of granulopoiesis and erythropoiesis, as well as in identifying left shift and nuclear abnormalities of megakaryocytes. Present study findings are in correlation with those of Gianelli U et al., who also stated that this discordance could be reduced by using myeloid and erythroid-specific immunohistochemical markers or by simultaneously evaluation of bone marrow aspiration and biopsy slides [6]. Many authors opined that this discordance could be attributed to variability

in quality of processing and staining [3,6]. For improving agreement in terms of nuclear abnormalities of megakaryocytes, authors have suggested use of digital imaging, machine learning processes and megakaryocytic morphometric evaluation [9].

Limitation(s)

The limitations of the present study include small sample size, being a single-centre study (which may introduce selection bias), and the varying levels of experience among the three reviewing pathologists.

CONCLUSION(S)

The present study demonstrates a moderate level of agreement and reproducibility between different histological parameters and good sensitivity and specificity of bone marrow histopathology in identifying various MPNs and can be very useful in resource-poor settings and in the early stages of disease evolution. The study emphasises on performing bone marrow biopsy as a routine diagnostic test in cases which are suspected to have MPNs.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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- Manual Googling: Feb 07, 2025
- iThenticate Software: Feb 10, 2025 (9%)

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- For any images presented appropriate consent has been obtained from the subjects. Yes

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