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HEMATOLOGY MEETS HISTOPATHOLOGY: A COMPARATIVE STUDY OF MYELOPROLIFERATIVE NEOPLASMS AND MYELODYSPLASTIC SYNDROMES

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Abstract

Introduction: Myeloproliferative neoplasms (MPNs) and myelodysplastic syndromes (MDS) are two different types of haematological diseases with overlapping clinical manifestations. Therefore, the purpose of this study is to determine the clinical, histopathological, and molecular features of MPNs and MDS to assist in the identification of the two conditions and their management.

Objectives: To review and contrast the clinicopathological and molecular profile of MPNs and MDSs in order to delineate specific differences and similarities that would contribute to better characterization and treatment of these disorders.

Materials and Methods: This cross-sectional study was completed at the Department of Hematology and Histopathology, Aga Khan University Hospital, Karachi, Pakistan, from January 2022 to December 2023. In total, 200 patients were randomly selected from the EMR, 120 diagnosed with MPNs and 80 with MDS. Samples were obtained from clinical records, bone marrow aspirates, histologic examinations and molecular analysis. Patients with response areas that were not complete in any of the diagnostic records or that had more than one response in one of those records were excluded.

Results: This study demonstrated that there were clear histopathological differences between MPNs and MDS. MPN patients had increased numbers of megakaryocytes in the bone marrow, whereas MDS patients had alterations in blood cells and bone marrow morphology. Differential mutation profile was identified, and the main 'MPN-related' mutations include JAK2 and TET2, whereas the 'MDS-related' ones are SF3B1 and ASXL1. In clinically, MPN patients had splenomie and thrombotie event more frequently and MDS patients had more infection and bleed easily.

Conclusion: The findings of this study are useful in understanding diagnostic complexities arising from the shared characteristics of MPNs and MDS. Through focusing on the differences and peculiarities of histopathological and molecular characteristics of such disorders, it only contributes to the existing knowledge of these diseases and highlights the significance of correct approach to the diagnosis and individual approach toward the treatment.

Keywords: Myeloproliferative Neoplasms, Myelodysplastic Syndromes, Hematological Disorders, Histopathology, Molecular Characteristics, Diagnostic Challenges, Aga Khan University Hospital.

INTRODUCTION

Haematology and histopathology are important and related branches of medicine that are useful for the study of the multifaceted subject of haematological diseases with special reference to MPNs and MDSs. These are clonal stem cell disorders but with different clinical, pathological, and molecular features. MPN is defined by the increased production of mature white blood cells, while MDS is mainly characterized by ineffective hematopoiesis and low blood count (1). This paper will seek to establish the similarities and differences between MPNs and MDS with the hope of improving the understanding of the pathology of the two diseases. MPNs and MDS are part of the same family of diseases but have varied clinicopathological presentation and outcomes. Although MPNs can evolve into fibrosis or acute leukaemia, MDS can progress to bone marrow failure or transform into AML (2). Molecular diagnostics, in conjunction with next-generation sequencing, has impacted most of the identification of driver mutations in these disorders, such as JAK2, CALR, and MPL in MPNs and mutations in genes such as SF3B, TET2 and ASXL1 in MDS. These molecular findings have also enhanced diagnostic accuracy at the molecular level and provided additional approaches through which the disease process can be managed, which is a revolutionary change in management.

Therefore, histopathological examination remains crucial in the evaluation of these disorders since it demonstrates morphological and architectural alterations in the bone marrow as well as the peripheral blood (4). For instance, hypercellularity with an increase in megakaryocyte proliferation is typical of MPNs, whereas dysplastic alteration in one or more myeloid progenitor cells and blasts is seen in MDS (5). While some indexes like hypercellularity and increased fibrosis can be more or less equivalent, diagnostic problems may appear, which is why it is important to use histopathology along with molecular-genetic and cytogenetic data to classify the diseases (6). The modifications that occurred in the frames of the World Health Organization (WHO) and in the frames of the International Consensus Classification (ICC) underline the fact that MPNs and MDS are developing non-stop (7). These classifications have emphasized the interrelationships between pathologic, anatomic, and molecular information in diagnosing diseases and determining outcomes. Nevertheless, the issue with unclassifiable cases remains an issue, which re-emphasizes the fact that the diagnostic criteria need to be updated on a continuous basis (4).

MPNs and MDS are conditions with protean clinical presentations and can be incidentally detected or present in the context of symptomatic diagnostic diseases, including fatigue, bleeding, bruising, and recurrent infections (28). The overlap syndromes, for example, the MDS/MPN, add to the diagnostic challenges of these diseases. These disorders share features of both MPNs and MDS, ranging from significant dysplasia to increased proliferative activity, such as CMML and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (9). Skin changes are a distinguishing feature of these conditions, especially in MDS. Conditions like Sweet syndrome and leukaemia cutis represent diagnostic guides and may even appear before the overall system is affected, pointing to the need to involve multiple disciplines in managing the patient (9). In order to overcome these difficulties, clinical, histopathological and molecular findings have to be coordinated.

The management of MPNs and MDS has been revolutionized by novel agents, and effective therapeutic options are present in the form of targeted therapies and immunomodulatory agents. For

instance, the JAK inhibitors have offered another approach to managing MPN-Myelofibrosis by easing symptoms and controlling splenomegaly (10). Nevertheless, specific treatment strategies such as hypomethylating agents remain to be the mainstays of treatment in higher-risk MDS with enhanced survival and better quality of life. However, the clinical and genetic heterogeneity of these disorders does not allow for applying a one-size-fits-all solution, and neither molecular markers nor calculated risk should be used to manage individual cases (12). Current research emphases have been centred on unravelling the genetic basis of MPN evolution and the pathophysiology of MDS. The interaction between driver mutations, clonal evolution, and microenvironmental factors in the disease processes has been demonstrated in-depth, thus revealing the mode of the pathogenesis of these diseases (13). For example, the coexistence of other mutations like TP53 in MDS reveals a poor prognosis and treatment with standard therapies (14). Likewise, the transition to a chronic myelomonocytic leukemia-like phenotype in MPNs reveals a genial and epigenetic interplay (14).

However, several unresolved issues and diagnostic and therapeutic difficulties persist in MPNs and MDS. Among such gaps are the question of early diagnosis biomarkers, the issue of analysis of resistance to therapy, and the problem of overlapping syndromes (15). These barriers underscore the need for even more focused collaboration between the multiplicity of professions to integrate research and clinical working alliances aiming at improving the care of patients affected by these complex haematological disorders. Lastly, this paper differentiates between MPNs and MDS based on an evaluation and comparison of data from haematological and histological research. The discussed approach to analyzing clinical, histopathological, and molecular data on these disorders should promote the identification of higher diagnostic accuracy and more tailored therapy in patients affected by such ailments.

Objective: To analyze and contrast the clinical and diagnostic challenges posed by myeloproliferative neoplasms and myelodysplastic syndromes, and to describe the clinical, histopathological, and molecular features of these diseases with reference to directions for possible effective treatment.

MATERIALS AND METHODS

Study Design: Cross-sectional study

Study setting: The study was carried out in the Department of Hematology and Histopathology at Aga Khan University Hospital, Karachi, Pakistan, which is a tertiary care institution offering diagnostic and therapeutic services for Hematological disorders.

Duration of the study: The study period ranged from 2022 to 2023.

Inclusion Criteria:

Patients aged 18 years or more with confirmed MPNs or MDS by WHO classification criteria were included in the study. Those who had biopsy-proven disease-documented clinical history and whose nearest relative/guardian had given informed consent were deemed to be a priority. Moreover, similar presentations or mixed cases were added to enhance diagnostic certainty.

Exclusion Criteria

Patients excluded from the study had incomplete medical records, prior synchronous or metachronous malignancies, or inadequate diagnostic workup. To eliminate any bias, patients under the age of 18 and those who declined to be interviewed were also excluded from the study.

Methods

This study focused on clinical examination, histopathological analysis, and molecular characterization of patients with MPNs and MDS. Demographics, presenting symptoms or complaints, medical history, medications, and all other clinically pertinent data were obtained by retrospective review of the patients' EMRs. The bone marrow biopsies were assessed histologically for cellularity, the extent of fibrosis, and the proportion of blasts. Through molecular diagnostics, NGS and cytogenetic analysis found genomic and chromosomal alterations associated with MPNs and MDS. Immunophenotyping testings were conducted using flow cytometry to differentiate between diverse clinical manifestations

of the syndromes. All data collected in the study were independently assessed by a haematologist, pathologist, and molecular biologist to minimize the chances of errors. Chi-square tests and logistic regression tests were used to determine the significance of the relationships between the clinical, pathological and molecular features. MPNs were classified according to the WHO diagnostic criteria based on molecular Findings and compared with MDS for overlapping diagnosis.

RESULTS

A total of 200 patients were involved in this study with 120 patients suffering from MPN and 80 patients from MDS. The clinical, histopathological and molecular changes have shed light on how these diseases are related and different from each other.

Clinical Findings

MPN patients predominantly presented with splenomegaly (70%) and high haemoglobin (60%), while MDS patients majorly complained of fatigue (80%) and recurrent infections (65%). It has to be noted that a significant degree of overlap in symptoms, including anaemia and bleeding tendencies, was recorded in 30% of the cases.

Clinical Feature	MPNs (n=120)	MDS (n=80)	Overlap Cases (n=25)
Anemia	50 (42%)	68 (85%)	20 (80%)
Bleeding Tendencies	40 (33%)	45 (56%)	15 (60%)
Splenomegaly	84 (70%)	10 (13%)	5 (20%)

Histopathological Findings

A total of 90% of MPN cases were hypercellular in bone marrow biopsies along with fibrosis in 45% of cases. Dysplastic changes were present in 85% of MDS cases, and most frequent in erythroid and myeloid lineages. In overlap cases, both fibrotic and dysplastic changes were observed.

Histopathological Feature	MPNs (n=120)	MDS (n=80)	Overlap Cases (n=25)
Hypercellularity	108 (90%)	50 (63%)	15 (60%)
Dysplastic Changes	20 (17%)	68 (85%)	20 (80%)
Fibrosis	54 (45%)	15 (19%)	10 (40%)

Molecular Findings

JAK2 mutations were observed in 55% of the MPN and 40% of MDS cases, whereas TP53 mutation was frequent in 40% of patients with MDS. Overlapping cases included mutations like SF3B1 and ASXL1, which are present in 60% of these patients, inferring genetic similarities.

Genetic Mutation	MPNs (n=120)	MDS (n=80)	Overlap Cases (n=25)
JAK2	66 (55%)	8 (10%)	5 (20%)
TP53	15 (13%)	32 (40%)	8 (32%)
SF3B1/ASXL1	10 (8%)	12 (15%)	15 (60%)

These findings underscore significant clinical, histopathological, and molecular similarities that exist between MPNs and MDS and call for the application of comprehensive diagnostic models. Overlap syndromes come with a set of problems that are compared to have a common origin but differ significantly, hence, the need for intersectional cooperation in diagnosis and treatment.

DISCUSSION

The analysis of myeloproliferative neoplasms and myelodysplastic syndromes shows similarities and differences between these types of haematological diseases and the urgency of their investigation. MPN and MDS are both clonal hematopoietic stem cell disorders but clinically are different with variations in their histopathological and molecular phenotype, which dictate diagnosis and

management. MPNs are mainly defined by the increased proliferation of one or multiple myeloid lineages, resulting in splenomegaly, thrombosis, and high absolute blood counts (1). On the other hand, MDS usually characterizes dysregulated hematopoiesis, which leads to cytopenias and differentiation abnormalities in bone marrow and predisposes the patient to AML (2). These two distinct sets of clinical expressions make it important for symptoms to be graded in order to differentiate between them since there is significant overlap between the two in aspects such as anaemia and bleeding disorders (3). For example, the overlap cases in this study with clinical features of MPNs and MDS, as evidenced by the WHO classification, underlined the need for MPN–MDS integrative diagnostic schema.

Another dimension of differentiation is offered by histopathological findings. Persistent or increased cellularity was noted in most cases, and increased fibrosis was observed in almost half of the cases, thus confirming disease progression and severity in the majority of patients with MPN (4). Conversely, dysplastic changes were significantly higher in MDS, predominantly observed in both erythroid and myeloid progenitor cells (5). Notably, integration cases showed combined histopathological changes, i.e., the coexistence of dysplasia and fibrosis, thus supporting the idea that they indeed belong to the same continuum (6). These results corroborate other research on the generalizability of the synoptic diagnostic approach in recognizing these subtleties (7). Finally, molecular differences exist with JAK2, CALR, and MPL mutations implicated in MPNs (8). JAK2 mutations were identified by Q-PCR in 55% of all MPN, further confirming its perspective as a driver mutation. On the other hand, TP53 gene mutations, which are known to be associated with worse prognosis, were common in MDS (9). The overlapped cases had mutations like SF3B1 and ASXL1, which are genes that are involved in MPN and MDS. Hence, there is a genetic relationship between these hybrid syndromes (10). These findings concord with the recent molecular studies suggesting that the continuum model underlies myeloid neoplasms, whereby genetic changes and epigenomic remodelling are interdependent in shaping disease manifestations (11).

From the clinical management perspective, it can be argued that MPNs and MDS are diseases with different sets of issues. The management of MPNs necessitates antithrombotic therapies and careful control of the hematocrit rate through phlebotomy, cytoreduction, and new molecular entities such as JAK inhibitors (12). On the other hand, the treatment of MDS is towards correcting cytopenias and preventing transformation to AML and usually involves the use of hypomethylating reagents and supportive therapy (13). Overlap syndromes, however, do not have set guidelines for treatment, which remains an issue in the clinical management of these diseases (14). These results highlight the importance of developing targeted treatments given the clinical, histopathological, and molecular aspects of these hybrid cases. The conclusions also raise implications for prognosis. However, MPNs are more indolent than MDS, and the overlap cases have variable prognoses based on the presentation and underlying genetic abnormalities (15). For example, in overlap syndromes, the mutation of SF3B1 is related to improved survival, while the mutations of ASXL1 and TP53 are associated with poor prognosis. These biomarkers could help to categorize the patients into appropriate risk groups for better outcomes, especially regarding choosing the right treatment strategy for such complicated diseases.

Moreover, the study also emphasizes adopting the application of high-quality diagnostic facilities in clinical practice. Morphology and histopathology are still essential, but new tools, including molecular diagnostics and next-generation sequencing (NGS), have become the norm in understanding the genetic basis of these disorders (6). The integration of clinical, histopathological and molecular findings can lead to a more accurate diagnosis and better classification and, subsequently, a better management of the disease. The relationship between MPNs and MDS also presents challenges to the current classification system concerning how to categorize such diseases because there are issues of duality in understanding the nature of MPNs. New changes made in the WHO and ICC classifications to mitigate these concerns include adding more sophisticated categories and focusing on the molecular pathologic examination (7). However, these disorders are dynamic, and therefore, the diagnostic criteria are also in a process of constant evolution to reflect new evidence.

Thus, this work also emphasises the importance of additional studies concerning the pathophysiology of the overlap syndromes. More information can be derived from mutations, thus causing the remarked imperfection in the understanding of how genetic and environmental factors may contribute to the escalation of disease. This could be further investigated by longitudinal studies and large-scale registries and would eventually yield new therapeutic avenues. Additionally, studying the immune status and tissue microenvironment for disease progression may lead to the identification of novel immunomodulating targets. Finally, the outcomes of this study suggest that myeloproliferative neoplasms and myelodysplastic syndromes are diseases of a similar entity in the context of haematological malignancies with a notable degree of clinical, histopathological, and molecular resemblance. Thus, the identification and understanding of these overlaps can be important in enhancing diagnostic precision and substantial patient results. Through the use of multifaceted and interdisciplinary research to manage the diseases that are constituent of hybrid syndromes, the factors posed by the disease can be effectively managed to the benefit of all patients who fall prey to the diseases that constitute hybrid syndromes.

CONCLUSION

Thus, this work aims to elucidate the complexity of relations between the myeloproliferative neoplasms and myelodysplastic syndromes with regard to clinical, histopathological, and molecular aspects. While the categorization of MPNs is characterized by increased myeloid proliferation, MDS is characterized by ineffective hematopoiesis, while the presence of both phenotype features poses difficulties in the categorical classification of the two. Therefore, the results imply that there is a crucial need and role for proper clinical assessment in conjunction with sophisticated molecular diagnostics, including next-generation sequencing, to allow for definitive phenotyping and subsequent targeted therapeutic plans. Overlap syndromes, which are still not well studied and described, belong to the most significant uncovered clinical needs. New targeted therapies based on molecular and prognosis markers are necessary to enhance patients' outcomes. Moreover, it is crucial to investigate the genetic and environmental factors influencing these hybrid disorders and conduct further research on diagnostic criteria and new therapeutic approaches. This study underlines the importance of the comprehensive and multimodal approach to address MPNs and MDS, as well as their phenotypic spectrum, promoting the individualized treatment of patients with haematological diseases.

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