DIAGNOSTIC APPROACH TO MYELOPROLIFERATIVE NEOPLASMS (MPNS)

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ABSTRACT

BACKGROUND

MPNs are caused by clonal proliferation of a pluripotent haematopoietic progenitor. They neoplasms are characterised by an excessive production of mature blood cells of myeloid lineage, which are independent and/or hypersensitive to cytokines for cell survival, proliferation and differentiation.

MATERIALS AND METHODS

The 2008 WHO classification system for haematological malignancies comprehensive and includes histology and genetic information. According to WHO (2008), MPNs are classified as follows-

Myeloproliferative Neoplasms (MPN), chronic myelogenous leukaemia, BCR-ABL I -positive, polycythaemia vera, primary myelofibrosis, essential thrombocythaemia, chronic eosinophilic leukaemia, not otherwise specified, mastocytosis, myeloproliferative neoplasms, unclassifiable.

RESULTS

Diagnosis of samples indicate that CML is the commonest MPN and in case of BCR-ABL1 negative MPNs, there is an increasing gamut of mutations, which are being discovered, nowadays. Hence, the diagnostic approach has to be updated slightly to carry out correct diagnosis of such mutations. Details of the suggested approach appears later in the article.

CONCLUSION

CML is the commonest MPN and in case of BCR-ABL1 negative MPNs, there is an increasing gamut of mutations, which are being discovered, nowadays. CALR is the 2nd frequently mutated gene in BCR-ABL negative MPNs.

Treatment and prognosis of MPNs are guided by their molecular characteristics. For e.g., imatinib is useful in case of BCR-ABL1 fusion gene defects and JAK2 inhibitors are effective in case of JAK2 mutated PV. CALR mutated MPNs have a better prognosis than other types of mutations. Thus, it is important to correctly diagnose the MPNs for better and accurate post-diagnosis treatment.

KEYWORDS

Chronic Myeloid Leukaemia (CML), Polycythaemia Vera (PV), Essential Thrombocythaemia (ET) and Primary Myelofibrosis (PMF).

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BACKGROUND

This chapter discusses contemporary diagnosis in Myeloproliferative Neoplasms (MPNs), which is according to the World Health Organization (WHO) system; this system is primarily based on morphology, but also includes information from cytogenetic and molecular studies. The WHO recognises five major categories of myeloid malignancies; one of these categories is MPNs, which comprise eight subcategories- Chronic Myeloid Leukaemia (CML), Polycythaemia Vera (PV), Essential Thrombocythaemia (ET), Primary Myelofibrosis (PMF), Systemic Mastocytosis (SM), Chronic Eosinophilic Leukaemia- Not Otherwise Specified (CEL-NOS), Chronic Neutrophilic Leukaemia (CNL) and MPN Unclassifiable (MPN-U). Bone marrow morphology is the cornerstone of specific diagnosis in MPNs.[1]

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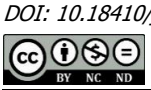


AIMS AND OBJECTIVES

Aim is to establish a decisive diagnostic approach to Myeloproliferative Neoplasms (MPNS).[2] All studies, experiments, study diagnosis collate to the following step-by-step approach to diagnosis.

MATERIALS AND METHODS

Criteria for diagnosis according to who (2008) CML-neutrophilic leucocytosis with a left shift, basophilia with BCR-ABL I mutation present. CML can be in a chronic phase, accelerated phase or blast crisis.

PV

Inclusion Criteria

1. Haemoglobin >18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume.

2. Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation.

Exclusion Criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation.
2. Serum erythropoietin level below the reference range for normal.
3. Endogenous erythroid colony formation in vitro.

ET

Diagnosis Requires Meeting all Four Criteria

1. Sustained platelet count ≥450 X^9/lt.
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis.[1]
3. Not meeting WHO criteria for polycythaemia vera, primary myelofibrosis, BCR-ABL1- positive CML or myelodysplastic syndrome or other myeloid neoplasm.
4. Demonstration of JAK2 V617F or other clonal marker or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis.[2,3,4]

PMF

Diagnosis requires meeting all three major criteria and two minor criteria.

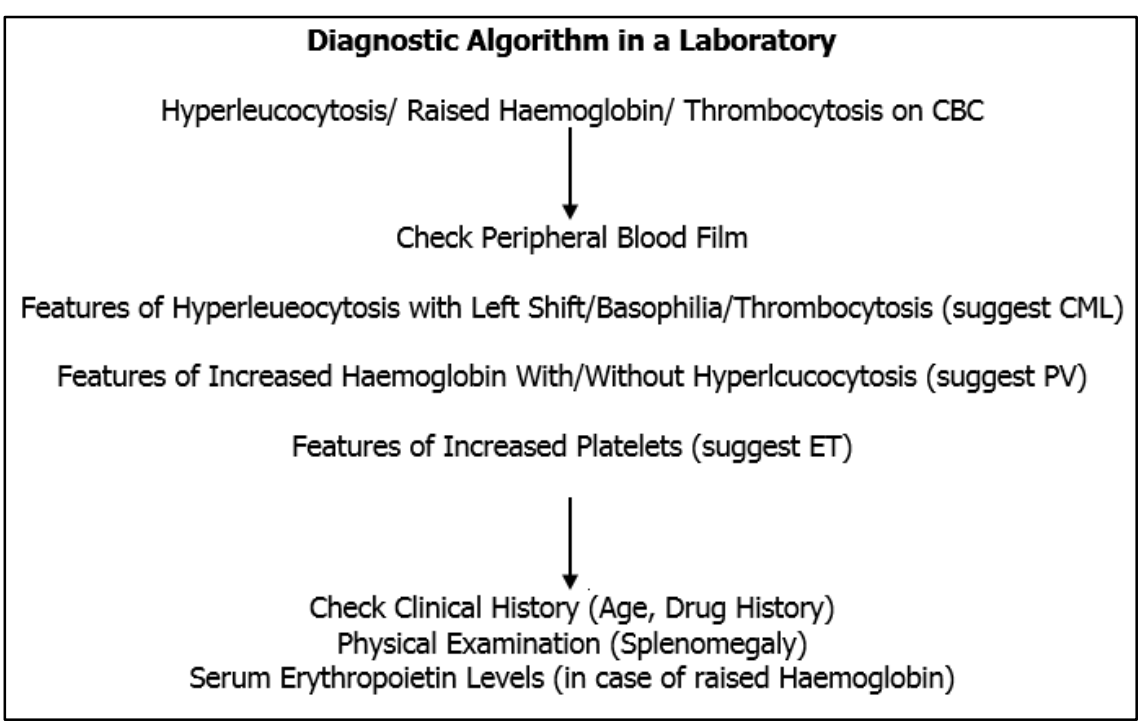
Major Criteria

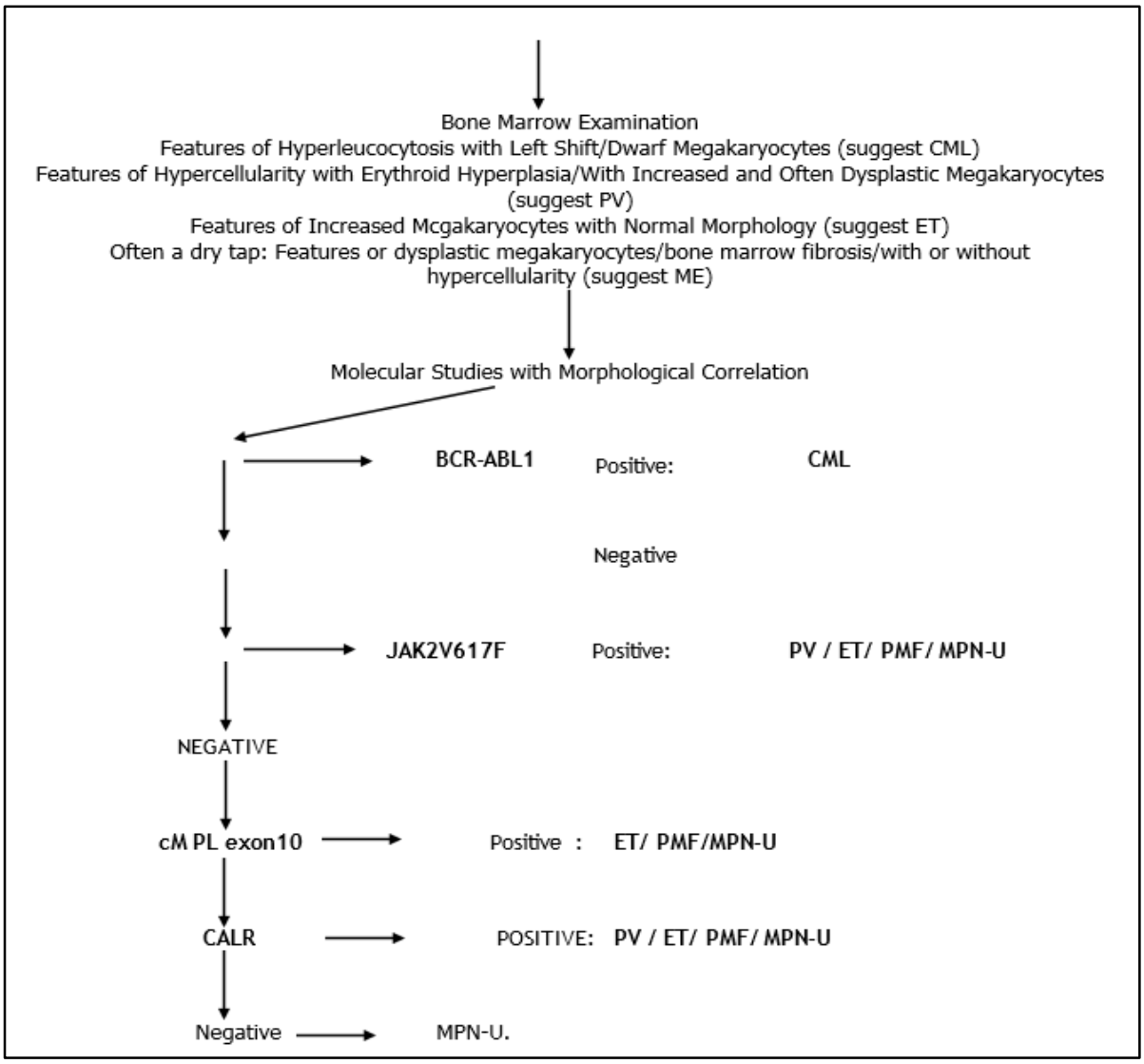
1. Presence of megakaryocyte proliferation and atypia usually accompanied by either reticulin or collagen fibrosis or in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease).
2. Not meeting WHO criteria for polycythaemia vera-BCR-ABL/positive chronic myelogenous leukaemia; myelodysplastic syndrome or other myeloid disorders.
3. Demonstration of JAK2 V617F or other clonal marker (e.g. MPLW 5 15KJL) or in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy or toxic (chronic) myelopathies.

Minor Criteria

1. Leukoerythroblastosis.
2. Increase in serum lactate dehydrogenate level.
3. Anaemia.
4. Palpable splenomegaly.

RESULTS





If all these tests are negative, some other mutations are tested. These mutations are the clonal markers in MPNs.

DISCUSSION

However, they are positive in only a minor percentage of MPNs. They are TET2, IDH1/2, DNMT3A, ASXL1, EZH2, CBL, SH2B3 (LNK), SF3B1, SRSF2 and U2AF1. JAK2 exon 12 mutations can also be performed (seen in 3% cases of PV).

CONCLUSION

CML is the commonest MPN and in case of BCR-ABL1 negative MPNs, there is an increasing gamut of mutations, which are being discovered, nowadays. JAK2 V617F is detected in 95% of PV and 60% of ET or PMF. Remaining 5% PV have JAK2 exon 12 mutation. Somatic mutations of MPL exon 10 (mainly codon W515) are found in 5% of ET or PMF. CALR mutations are found in 20%-25% of ET or PMF. CALR is the second frequently mutated gene in BCR-ABL negative MPNs.

Treatment and prognosis of MPNs are guided by their molecular characteristics. For e.g., imatinib is useful in case of BCR-ABL1 fusion gene defects and JAK2 inhibitors are effective in case of JAK2 mutated PV. CALR mutated MPNs have a better prognosis than other types of mutations. Thus, we can see the importance of correctly diagnosing the MPNs and the role of molecular genetics in the diagnosis, treatment and prognostication of the patients.[4,5]

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