How We Treat Myeloproliferative Neoplasms

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Abstract

The phildelphia-negative myeloproliferative neoplasms were defined based upon careful clinical review and an analysis almost a century ago. Increasingly this field is becoming more complex in terms of diagnostic information, treatment options have however been following behind. Here we present our approach to the management of these entities.

The present report focuses on management strategies for the myeloproliferative neoplasm according to the structure and processes we use within our center, a large tertiary unit in central London. The standard procedures for achieving an accurate diagnosis and risk stratification and therapeutic strategies for these diseases with a detailed focus on contentious areas are discussed. In the 9 years after the description of the Janus kinase 2 mutation, this field has altered quite radically in several aspects. For example, a new therapeutic paradigm exists, especially for myelofibrosis. We share how our unit has adapted to these changes.

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Achieving an Accurate Diagnosis

The recent advances in our repertoire of molecular tests and in our knowledge of the natural history of myeloproliferative neoplasms (MPNs) means that our diagnostic approach has become increasingly laboratory based and involves several disciplines, including cellular pathology, blood film morphology, molecular biology, and cytogenetics. The implication is that in clinical practice, the hematologist must be able to synthesize these data and accurately communicate the clinical scenario and questions. Unless this conversation occurs, the risk of inaccurate diagnosis and overinterpretation of a single piece of the diagnostic puzzle will be unacceptably high. An example of the flow process that we follow for classic MPN is shown in Figure 1. To achieve a diagnosis of MPN, the exclusion of underlying reactive conditions has been simplified by the expanding repertoire of molecular abnormalities, which has been exemplified by the recent description of calreticulin (CALR) mutations.[1,2] These secondary causes are listed in a footnote to Figure 1. Having excluded a reactive disorder, it would be ideal to use as much diagnostic information as possible to be able to assign the patient to a particular category of MPN. Although the MPN unclassified category exists, the information to make robust management recommendations for this entity is insufficient. It is important to note that although the molecular abnormalities identified in MPN likely define a neoplastic process, they are not specific to the subtype of MPN.

Although the recent iterations of the World Health Organization diagnostic criteria are welcome, in some areas, difficulty and controversy remain. One example is in discriminating between Janus kinase 2 (JAK2) Val617Phe (V617F)-positive essential thrombocythemia (ET) and polycythemia vera (PV). This is clearly an important issue owing to the different management strategies for these diseases and the importance of controlling the hematocrit in PV. A recent report from a well-respected Spanish group illustrates these difficulties perfectly and highlights the British Committee for Standards in Haematology diagnostic criteria of PV[3] (Table 1), as the most sensitive and specific criteria.[4] The report from Alvarez-Larran et al[4] deserves additional mention because of their work to evaluate the diagnostic accuracy of the histologic features and to assess its correlation with the presence of mutations and clinical outcomes. Two pathologists reviewed the bone marrow biopsies corresponding to 211 patients with MPN. They reported that the specificity of the histologic findings was 100%, 98.5%, and 98% for PV, ET, and primary myelofibrosis (PMF), respectively. However, the sensitivity of the histologic diagnosis was low for PV and ET (32.5% and 54%, respectively) and acceptable for PMF (75%). Of 146 patients with clinical ET, 13 (9%) were diagnosed with prefibrotic PMF. Regarding the issues with

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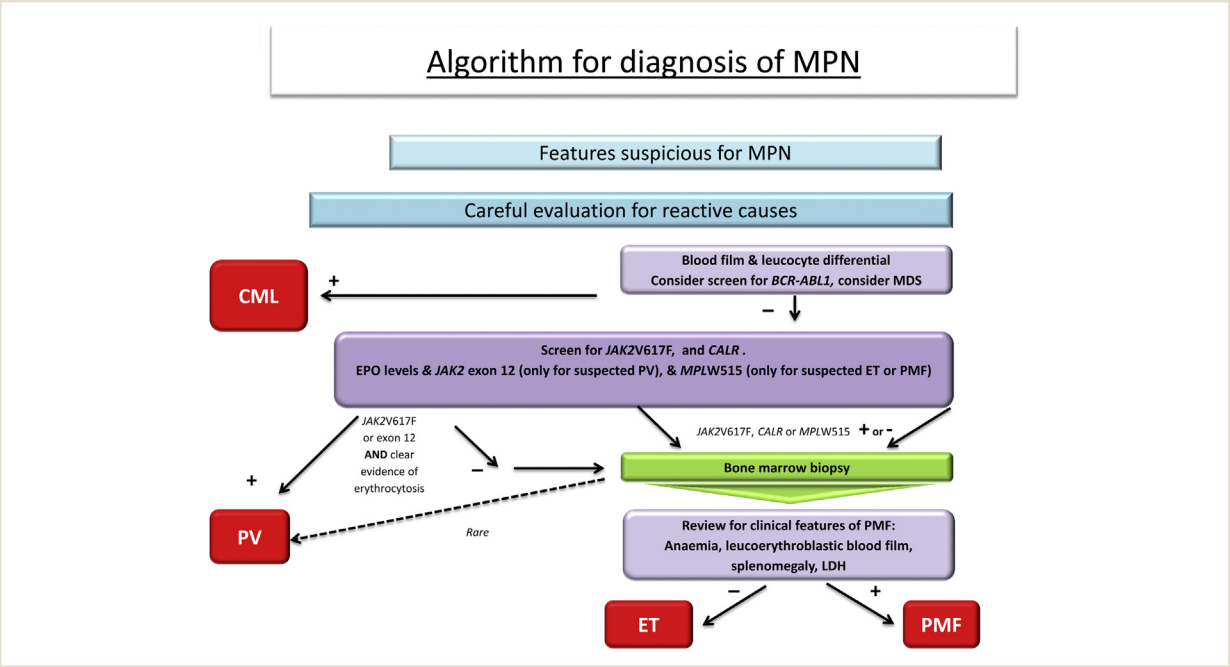
Figure 1 Algorithm for Diagnosis of Myeloproliferative Neoplasms



Abbreviations: CALR = calreticulin; CML = chronic myelogenous leukemia; EPO = erythropoietin; ET = essential thrombocythemia; LDH = lactate dehydrogenase; MDS = myelodysplastic syndrome; PMF = primary myelofibrosis; PV = polycythemia vera.

discriminating PV from ET, other investigators have also suggested using a hematocrit level close to that recommended by the British Committee for Standards in Haematology, because it improves the diagnostic accuracy.[4] One of the major difficulties inherent in discriminating between ET and PV is the limited availability of red blood cell mass testing. Alvarez-Larran et al[4] was also one of several groups to highlight that the entity of prefibrotic MF remains controversial, and additional international collaboration and educational efforts are widely acknowledged to be required.[5,6] Specifically, the issues concerning the discrimination of ET and prefibrotic MF revolve around the reproducibility of the specific histologic features, predominantly megakaryocyte abnormalities, which enable discrimination of these entities. The incorporation of clinical criteria (ie, anemia, leukoerythroblastic blood film, and splenomegaly) are important. The major clinical differences in outcomes and the management strategy for patients with ET (the most indolent MPN) compared with those with PMF (the most aggressive MPN) highlight the importance in achieving an accurate diagnosis.

To achieve as accurate a diagnosis as possible, our team have used the document "Improving Outcomes Guidance" mandated in the United Kingdom (available at: www.nice.org.uk/Guidance/CSGHO) in facilitating a multidisciplinary conversation, which is hosted by a video conference across several different hospital sites and involving all the contributing disciplines. This also enables us to perform a coordinated management decision and to discuss the options potentially available at different sites (eg, clinical trials). Patients with refractory or progressive disease can also be discussed at this meeting. Patients with MPN, chronic and acute myeloid leukemia, myelodysplasia, and other bone marrow failure disorders are discussed in a myeloid-specific setting.

Other general management approaches are available. The National Institute for Health and Care Excellence guidance also incorporates the role of clinical nurse specialist in the management of chronic conditions such as MPN. This role is a cornerstone of management in our service, because the clinical nurse specialist is the key point of contact, information, and support for the patients and their families. In our service, many stable patients are reviewed by the clinical nurse specialist by telephone interview or in separate clinics, with a consultant or medical review annually. The role is also critical because of the flux of staff that is often seen in at inner city tertiary service to provide continuity for patients beyond that of the consultant physician and education for the nursing and other staff. This infrastructure is also critical to incorporating symptom assessment for these patients, because it is an increasingly important aspect of care. In addition to this role, we also have a prescribing pharmacist present in the clinics available to assess and provide prescriptions for stable patients and as a source of expert pharmacy advice for the clinicians.

Management of ET and PV

The treatment of those with ET and PV is considered jointly in this section, although clearly differences exist in the natural history and clinical manifestations. These patients will undoubtedly benefit from aggressive risk management for vascular disease. We use low-dose aspirin for these groups of patients. However, although this is evidence-based medicine for PV in accordance with the findings from the European collaboration on low-dose aspirin in polycythemia vera (ECLAP) study,[7] aspirin remains controversial for