Coexistence of Myeloproliferative Neoplasm and Plasma-Cell Dyscrasia

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Abstract

Introduction: Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), and are characterized by clonal proliferation of hematopoietic cells in the bone marrow. There are numerous case reports and reviews reporting patients with coexisting MPN and plasma-cell disease such as multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS). **Methods:** We report 15 patients treated at our institution over a 5-year period (January 2008 to December 2012) with a diagnosis of both an MPN and MGUS or MM. We also reviewed and summarized published case reports and studies describing the coexistence of these two disease entities. **Results:** Most patients (12/15) had an MPN diagnosis made before or at the same time as the MGUS/MM diagnosis. Eventually, 2 patients developed a lymphoid leukemia, 1 patient developed lymphoma, and 1 patient developed acute myeloid leukemia, raising the question of whether patients with coexistence of myeloid- and lymphoid-derived neoplasms are more prone to leukemic or lymphomatous transformation. We did not find any treatment-related effect that could have contributed to the development of coexisting MGUS or MM and MPN. Of the 7 patients with an abnormal karyotype, 3 patients had trisomy 8. **Conclusion:** At present, management strategies are aimed at treating the MPN and regularly monitoring the MGUS for transformation to an overt plasma-cell malignancy. However, for patients who develop overt MM, management is focused more on treating the myeloma and monitoring the MPN. It has not yet been definitively shown that these 2 entities arise from a common-ancestor hematopoietic stem cell.

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Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[1,2] These 3 chronic hematologic neoplasms are characterized by clonal proliferation of hematopoietic cells in the bone marrow (BM).[1,3] PV is characterized by a hypercellular BM that results in increased numbers of erythroid, megakaryocytic, and granulocytic precursor cells and an absolute increase in hematocrit. ET is characterized by an increase in the number of megakaryocytes in the BM with atypical nuclei, resulting in an increase in the number of platelets in the peripheral blood. PMF is characterized by variable BM cellularity, increased reticulin and collagen BM fibrosis, the presence of peripheral blood leukoerythroblastosis, cytopenias, and progressive splenomegaly.[1] The annual incidences of both PV and ET are approximately 1 to 3 cases per 100,000 persons,[4] whereas the incidence of myelofibrosis (MF) is approximately 1 to 2 cases per 100,000 persons.[5]

Almost all patients (> 95%) with PV have the acquired Janus kinase 2 gene (*JAK2*) V617F mutation.[6,7] The frequency of *JAK2* V617F in patients with ET and MF has been reported to be approximately 55% and 65%, respectively.[3] The major complications of the Philadelphia chromosome-negative MPNs include the propensity to develop arterial and venous thrombosis, the propensity to hemorrhage, and the risk of leukemic transformation.[1] The 10-year rate for transformation to MF is < 1% for ET[8] and < 10% for PV.[9] The 10-year rate for leukemic transformation is < 1% for ET[8] and < 5% for PV.[9] MF has a higher rate of leukemic transformation, with the 5-year rate of transformation ranging from 6% in low-risk to 21% in high-risk patients.[10]

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Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is defined as the presence of a monoclonal protein without features of multiple myeloma (MM) or other related malignant plasma-cell disorder such as Waldenström macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia.[11,12] In a recent population-based study, the prevalence of MGUS in the general population was reported to be 3.2% in patients older than 50 years of age and 5.3% in those older than 70 years of age.[13] MGUS is usually detected after a routine blood test reveals an elevated total protein concentration and subsequent workup including serum protein electrophoresis confirms a monoclonal spike.[12] A monoclonal protein concentration < 3 g/dL, the absence of immunoglobulin light chains in the urine, a BM aspirate with $< 10\%$ plasma cells, and the absence of end organ damage associated with MM (osteolytic lesions, anemia, hypercalcemia, and renal insufficiency) are consistent with the diagnosis of MGUS. In contrast, a monoclonal protein value ≥ 3 g/dL, at least 10% plasma cells on examination of the BM, or both, in addition to clinical features of MM as mentioned above indicate a diagnosis of MM. Patients who meet these criteria, but have none of the clinical features as listed above are considered to have smoldering myeloma. If the monoclonal protein and the percentage of plasma cells in the BM are consistent with MGUS and there is concomitant nephrotic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, carpal tunnel syndrome, massive hepatomegaly, or any combination of these, the most likely diagnosis is primary amyloidosis resulting from the deposition of light chains in organs and tissues.[14]

The probabilities of MGUS transforming into one of the malignant plasma-cell disorders are 17%, 34%, and 39% at 10, 20, and 25 years of follow-up, respectively.[15] A strong predictor of progression is the serum monoclonal protein concentration.[15,16] In a large series of 1384 patients with a median follow-up of 15.4 years, the actuarial risks of progression at 20 years were 14%, 25%, 41%, and 49% for monoclonal protein concentrations of 0.5, 1.5, 2.0, and 2.5 g/dL, respectively.[17] There is evidence to suggest that the MGUS clone is already malignant at the time of its initial appearance.[18,19] In fact, the clonal plasma cells of patients with MGUS show a phenotypic profile similar to that of MM plasma cells (CD38 positive [$CD38^+$], $CD56^+$, and $CD19^-$), although the proportion of phenotypically normal plasma cells is higher in patients with MGUS than in those with overt myeloma.[20] Thus, there are 2 populations of plasma cells in persons with MGUS: 1 is normal and polyclonal ($CD38^+$, $CD56^-$, $CD19^+$), and the other is clonal and has an abnormal immunophenotype ($CD38^+$, $CD56^+$, $CD19^-$).

It is also important to recognize that BM fibrosis can occur in the setting of plasma-cell dyscrasias as a secondary event and this secondary or reactive process in itself is not the same as an MPN.[21-24] In fact, increased BM fibrosis in the setting of MM correlates with poorly differentiated plasma-cell morphology and is associated with a worse prognosis.[25]

Coexistence of MPN and MGUS

In a prospective study conducted in 61 MPN patients (median age 62 y) in Greece from 1982 to 1987 by Economopoulos et al.,[26] 8.2% ($n = 5$) of patients were found to have coexisting MGUS, which is higher than the prevalence reported in the general population at approximately 1% to 3%.[27,28] Of these 61 patients, 37 had a Philadelphia chromosome-negative MPN (15 PV; 7 ET; 11 MF; 4 unclassifiable); 24 patients had chronic myeloid leukemia (CML). As all 5 patients with MGUS had Philadelphia chromosome-negative MPN; the prevalence of MGUS was 13.5% in the subgroup of patients with Philadelphia chromosome-negative MPN. Cesana et al. enrolled 1231 patients with MGUS or smoldering MM to study the factors associated with malignant transformation and reported that 0.4% of these patients had an MPN at the time of diagnosis.[16]

However, other studies have not shown a higher prevalence of MGUS/MM in patients with MPN.[29,30] Duhrsen et al. conducted a retrospective analysis of 199 patients with an MPN in Germany (treated between 1980 and 1985; mean age 52.8 y).[29] Of the 48 patients with MF, 3 had a concomitant MGUS. However, none of the 35 patients with PV and 42 patients with unclassifiable MPN were found to have coexisting MGUS. Randi et al. conducted a retrospective study of 382 patients with ET and PV in Italy over a 23-year period (median follow-up, 6.83 y). The mean age of the study participants was 54.75 years.[30] The study included 164 patients (92 males and 72 females) with PV and 218 (78 males and 140 females) with ET. An age- and sex-matched cohort of 500 patients served as a control population. The presence of monoclonal protein (M protein) was sought at the time of diagnosis and later during follow-up. M protein was found in 14 patients with MPNs, representing 3.6% of patients with ET or PV, and in 10 participants of the control group (2%). The occurrence of M protein in PV and ET did not differ significantly from that observed in the control group, and no significant statistical difference based on age was observed.

Case reports and case series of MPNs and gammopathies in the form of MGUS and MM have been reported, and in some cases an additional diagnosis of lymphoma has occurred as well.[31-34] Two patients with PV who then developed MM had received prior radiation treatment to the sternum for PV,[35,36] and 3 had received phosphorus-32 (P32) as part of their PV therapy.[37-39] Two patients with ET developed MM after receiving hydroxyurea;[40,41] another patient had received P32,[42] thioTEPA,[43] and busulfan before the onset of MM.[44] One patient developed MF after he received single-agent cyclophosphamide therapy for MM,[45] although 2 other patients with MM developed MF without any cytotoxic treatment.[46,47] A single case report of a patient with MGUS who developed an unclassifiable MPN after treatment with thalidomide and a monoclonal antibody to CD20 (rituximab) has also been reported.[48]

Patients With MPN and MGUS at Our Institution

In Table 1, we have described 15 patients at our institution with a diagnosis of both an MPN and MGUS/MM. Ninety MPN patients seen at the Mount Sinai Medical Center between the years 2008 and 2013 were identified randomly through a billing-code screen. Of these patients, 32 were noted to have documented serum or urine immunofixation studies in the electronic medical record. Of these 32 patients, a total of 15 were identified to have coexisting MPN and MGUS/MM. The reasons or indication for testing for the presence of a monoclonal gammopathy in a fraction