Case Report

Myeloproliferative Disease: Dealing With a Diagnostic Dilemma

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Abstract

Myeloproliferative neoplasms (MPNs) constitute a group of hematologic clonal diseases that affect one or more myeloid lineages with abnormal proliferation. It is rare disease entity and incidence is about 1.15 to 4.99/100 000 person-years among hematological neoplasms for all subtypes of MPNs combined. Patients who present with hepatosplenomegaly, hyperleukocytosis with monocytosis should have routine tests along with bone marrow morphology possibly biopsy, quantiferon TB Gold in tube test, Dengue fever IgM, IgG, NS-1 antigen, cytogenetics t(9;22), BCR cABL fusion gene, JAK-2 V617F, MPL mutations, CALR gene test done along with karyotyping and flowcytometry to evaluate and establish diagnosis towards management.

Key words: Myeloproliferative disease, BCR-ABL fusion gene, (JAK 2) V617F mutation, Calreticulin (CARL), Tuberculosis

Introduction

Myeloproliferative diseases was determined by William Dameshek in 1951, including chronic myeloid leukemia (CML), Polycythemia vera (PV), Essential thrombocytopenia(ET), Primary myelofibrosis(PMF) and Erythroleukemia.[1] Philadelphia(Ph) chromosome (short 22 chromosome) was discovered by Peter Nowell and David Hungerford in 1960.[3] Myeloproliferative neoplasms (MPNs) constitute a group of hematologic clonal diseases that affect one or more myeloid lineages with abnormal proliferation4 and it is a rare disease entity with incidence 1.15 to 4.99/100,000 person per years.[2]

Case report

We report a case of a 47 year old gentleman presented with a five day history of abdominal distension, nausea and generalized body ache and he was admitted in a hospital abroad. On the second day of admission he had developed disorientation and abnormal movements of the limbs. He was shifted to ICU and had treated there with electrolytes supplementation, parenteral antibiotics (ceftriaxone). In thorough investigations done at the hospital, hyperleukocytosis, monocytosis, elevated liver enzymes and hepatosplenomegaly in Ultrasound were found. Bone marrow aspiration cytology was consistent with chronic myeloproliferative disease. Cytogenetic test, t (9; 22) was found to be negative and other relevant cytogenetic tests were also turned to be negative. Dengue fever IgM, IgG, NS 1 antigen were also negative. Blood tests for Quantiferon-TB Gold in tube test was asked for screening analysis for infection by M. tuberculosis was not conclusive and stool routine examination was also unremarkable.

His detail clinicopathological reports were as follows:

- Hgb: 10.8g%, RBC: 3.83 million/cu mm, Hematocrit: 32%, MCHC: 34%, MCV 84 fl, MCH: 28.7 pg
  Platelates counts: 450000 cubic mm, WBC: 129800 cubic mm, Band: 26%, Metamyelocyte: 25%
- Bilirubin conjugated- Direct: 2.2 mg/dl, Indirect :2.09 and total 4.29 mg/dl (if *by 17.1 gives micro mol per lit)
- Glu Random: 109mg/dl
- BUN & Cr: within normal limit

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Electrolytes; Na+ 140 meq/l, K+ 2.28 meq/l
Stool RME: Erythrocytes +ve, Fungi +ve, Undigested food particle: +ve, culture -ve

- Urine: Erythrocytes 6-8
- AST 115 U/L ,ALT 123 U/L
- Alk Ph 157U/L
- Dengue fever IgM, IgG –ve
- NS(Nonstructural Protein)1 antigen -ve
- PBS: monocytosis (20% monocytes), DD: TB
- Diagnosis of infectious tuberculosis - Quantiferon - TB gold IT: cannot be interpreted due to the insufficient production of interferon
- Interferon gamma production: NC 0.01IU/ml, Ag TB-NC 0.000IU/ml, Positive control-NC 0.08IU/ml.
- USG abd: Enlarged spleen and liver with minimal ascites.
- X-ray Chest: Left basal atelactatic shadowing
- Bone marrow showed 20% monocytes Chronic Myeloproliferative Disease, Part of DD: CMML
- Cytogenetic test: t(9;22) or translocation or numerical variant characteristics of CMML or MDS were all absent, which were as follows:
  - CMML- loss of Y chr, trisomy 8 monosomy 7 or del- 7, del- 20, complex karyotype Ph – chr -ve, t(5;12) Flow - CD 14, CD 15, CD 24
  - MDS- del- 5, monosomy 7, del- 7, trisomy 8, del-20

In such scenario, Chronic Myelogenous Leukemia (CML) cannot be confirmed; however, in view of the presence of peripheral blood absolute monocytosis and presence of 20% monocytes in the bone marrow smears, the diagnosis of Chronic Myelomonocytic Leukemia (CMML) should be considered as part of the differential diagnosis. The absence of any specific translocation or numerical variant characteristic of CMML or Myelodysplastic Syndrome(MDS) suggest the need for close follow up of the patient and repeating the bone marrow in 4-8 weeks after ruling out other causes for monocytosis primarily tuberculosis. Diagnosis of the patient was Chronic Myeloproliferative Disease. He was kept on close follow up monthly with hemogram and bone marrow examination report. He was lost to follow-up and was later died in several months.

Discussion

Myeloproliferative neoplasms (MPNs), a rare disease entity was possible to classify MPNS as Ph-negative and Ph-positive, in 1996, Brian Druker discovered Imatinib, a tyrosine kinase inhibitor (TKI) considered a novel agent in the treatment of CML.[5] Janus kinase (JAK) 2 V617F mutation was described in several laboratories[7], [10] which appeared in Ph–negative MPNS, subsequently MPLW515 L mutation described in 2006.[6]

The most commonly recognized mutation in the remainder of the MPNs is JAK2 V617F, and it is presented in greater than 90% of patients with PV and approximately half of those with PMF or ET. This mutation substitutes phenyl alanine for valine at position 617 in the JH2 domain (Val 61phe,V617F) of exon fourteen, leading to constitutive activation of the JAK-STAT and other pathways resulting in uncontrolled cell growth. The presence of these mutations is determined by PCR assays and may be helpful in differentiating a MPNs from a reactive cause of elevated counts. [7,8,10] More recently, Calreticulin (CALR) gene was also described in 2013. These findings resulted into understanding of the disease and development of novel agents for treatment. [10]

World Health Organization (WHO) classified hematopoietic and lymphoid tissue tumors with genetic information in 2001[15]. The classification published in 2008[11] and in 2017, consecutively with revision in genetic and molecular aspects. This approach is step forward for standard diagnosis of MPNs throughout the world.[4]

The WHO currently classified the MPNs into seven categories: Chronic Myeloid Leukemia (CML), Chronic Neutrophilic Leukemia (CNL), Polycythemia Vera (PV), Essential Thrombocythemia (ET) , Primary Myelofibrosis(PMF), Chronic Eosinophilic Leukemia not otherwise specified (NOS) and Unclassifiable Chronic Myeloproliferative Neoplasms (MPN-U). Mastocytosis is no longer included in that group.[4]

Among Ph-negative MPNs, the most common ones include PV,ET and PMF, share JAK 2V617F gene, thrombopoietin receptor gene-myeloproliferative leukemia-MPL or CALR gene mutations as well as cytogenetic abnormalities.[4, 13]

Despite these advances, bone marrow morphological evaluation remains an important diagnostic tool[13], though they are not unique to these conditions and may be present in the other neoplasms.[4] WHO diagnostic criteria of 2016 for MPNs (PV, ET, prefibrotic PMF and overt fibrotic PMF) and updated review 2016 includes the differentiation should be used.[4, 13, 14]

Conclusion

In patients, those presented with hepatosplenomegaly and hyperleukocytosis or monocytosis, apart from obtaining baseline studies, a bone marrow examination followed by cytogenetic test especially t(9;22) and mutations like BCR-ABL fusion gene, (JAK 2) V617F and Calreticulin (CALR) is also mandatory.

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