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Review

A REVIEW OF BCR ABL1 NEGATIVE MYELOPROLIFERATIVE NEOPLASM WITH DENTAL IMPLICATIONS

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ABSTRACT

BCR-ABL1 negative myeloproliferative neoplasms (MPN) primarily include: Essential thrombocythemia (ET), Polycythemia vera (PV), and Primary myelofibrosis (PMF). They are considered rare hematological malignancies. Lately, with ongoing advances in the field of genetics and molecular biology, more clarity has been achieved on the pathogenesis of these disorders and many advances are being made in the diagnosis, prognostic evaluation and treatment of these malignancies. These disorders have oral manifestations and also present a significant risk of bleeding and thrombosis after dental procedures if proper precautions and care are not taken. This article highlights important aspects of these disorders including oral manifestations and dental care.

1. Introduction

Hematologic malignancies are one of the top 10 malignancies with respect to incidence and mortality.[1] Myeloproliferative neoplasms (MPN) are malignant clonal hematopoietic stem cell neoplasms characterized by the sustained proliferation of one or more cell lineages of myeloid, erythroid, or megakaryocytic origin.[2] They are marked by the excessive production of terminally differentiated blood cells that are fully functional.[3]

The classical BCR-ABL1 negative myeloproliferative neoplasms (MPN), include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) and in 1951, William Dameshek classified them as "myeloproliferative disorders" (MPD).[4] The term "neoplasm" was suggested in regard to these disorders in 2008 to signify the clonal nature of these myeloproliferative disorders.[5]

MPNs are categorized as rare cancers, as their incidence is lower than 6 per 100,000 persons per year. Incidence of PV ranges from 0.4 to 2.8, ET from 0.38 to 1.7, and PMF from 0.1 to 1.0 per 100,000 persons per year.[6] Epidemiological data on the incidence and prevalence of MPNs in India, are sparse.[7]

2. WHO (World health Organization) classification of MPN 2016 [8]

- Chronic myelogenous Leukemia, BCR-ABL 1- positive (*Breakpoint cluster region – Abelson 1)
- Chronic neutrophilic leukemia
- Polycythemia vera

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- Primary myelofibrosis
- Primary myelofibrosis, prefibrotic/early stage
- Primary myelofibrosis, overt fibrotic stage
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- Myelo proliferative neoplasm, unclassifiable

3. Genetics

Chronic myelogenous leukemia (CML) is the only MPN which is characterized by the presence of the *BCR-ABL* fusion gene and due to its unique pathogenesis and treatment, it is considered separately from the rest of the MPNs.[9]

With overlapping features, PV, ET, and PMF are categorized as Philadelphia-negative classical MPNs.[6]

3.1 JAK2

The Janus kinase 2 (JAK2) V617F, is present in 95-97% of patients with PV and 50-60% of patients with PMF and ET.[8] Here, there is substitution of phenylalanine for valine at position 617 in the JH2 domain (Val617Phe, V617F) of exon 14, which leads to constitutive activation of the JAK-STAT and other pathways resulting in uncontrolled cell growth.[9] Additional mutations within exon 12 of JAK2 are found in approximately 3-4% of patients with PV.[10]

3.2 MPL

The MPL (myeloproliferative leukemia virus) oncogene encodes for the TPO-R (thrombopoietin receptor) MPL, which signals through JAK2 and is considered essential for megakaryopoiesis. MPL mutations have been reported in 4% of patients with ET and 5% to 9% of patients with MF.[10]

3.3 CALR

CALR mutations are found in 20-25% of patients with ET and PMF.[10]

These three "driver mutations" are often mutually exclusive, meaning that if one is present the others are absent.[9]

Approximately 10% to 15% of patients with PMF or ET do not express any of the 3 mutations and are referred to as being “triple negative”.[11] This is associated with relatively adverse survival rates, particularly in PMF patients. In these patients, somatic mutations in both *JAK2* exon 14 and MPL exon 10, often at the same codon as the more common mutations, are sometimes noted.[12]

Sometimes, there is concomitant presence of other mutations in JAK2, MPL, or CALR mutated MPN, the pathogenetic role of which is thought to involve co-operation with driver mutations primarily affecting cytokine signaling, further disrupting the epigenetic or transcriptional regulation. The higher prevalence of some of these mutations e.g. ASXL1(Additional sex combs like 1), TET2 (Ten-eleven translocation oncogene family member 2), IDH1 (Isocitrate dehydrogenase 1) , IDH2 (Isocitrate dehydrogenase 2), DNMT3A (DNA methyltransferase 3 alpha), SF3B1 (Splicing factor 3B subunit 1), TP53(tumor protein p53), in blast-phase MPN suggests a role in disease progression or transformation into AML (Acute myeloid leukemia).[11]

Also, mutations in an adaptor protein LNK (lymphocyte adaptor protein) occur in MPNs and may account for increased cellular proliferation.[13]

Evaluation of MPNs involves comprehensive hematological/laboratory workup, bone marrow (BM) biopsy, cytogenetic analysis, and clinical assessment and a set of specific WHO criteria which take into account all of these factors.[8, 14]

4. Polycythemia vera

Polycythemia vera is a clonal neoplasm characterized by the overproduction of mature red blood cells. Myeloid and megakaryocytic elements are also often increased.[9]

4.1. Epidemiology

The median age at diagnosis of approximately 60 years, but the disease can also be seen in young people. There is a slight male preponderance (1.2:1) and the disease is more common in Ashkenazi Jews. [15] Familial PV has been associated with mutation of the erythropoietin (EPO) receptor.[9]

4.2. Pathophysiology

The primary pathology revolves around a pluripotent stem cell capable of differentiating into red blood cells, granulocytes, and platelets by the activation of the JAK-STAT pathway. Erythroid precursors in PV are extremely sensitive to erythropoietin, leading to increased red blood cell production. This leads to an increased red cell mass and increased blood viscosity, which can then lead to arterial or venous thrombosis, bleeding, or both. Increased hematocrit increases the chances of thrombotic events. A reduction in cerebral blood flow in patients with hematocrits of between 53% and 62% has been demonstrated. Increased production and breakdown of blood cells can lead to hyperuricemia and hypermetabolism.[9]

4.3 Signs and symptoms

Patients may be asymptomatic at the time of diagnosis; however, most patients develop symptoms as the hematocrit and/or platelet counts increase. Elevated hematocrit is associated with symptoms of hyperviscosity including headache, blurred vision and plethora. Thrombosis in small blood vessels can lead to cyanosis, ulceration, or gangrene in the fingers or toes. There are chances of myocardial infarction, deep venous thrombosis, transient ischemic attacks, and stroke because of thrombosis in larger vessels. A cerebrovascular event leads to diagnosis in 35% of patients with PV. Increased blood cell turnover can cause hypermetabolism which can in turn lead to hyperuricemia, gout, stomach ulcers, weight loss, and kidney stones. As the disease progresses, many patients develop abdominal pain secondary to splenomegaly.[9]

The peripheral smear in PV shows an excess of normochromic, normocytic RBCs. However, if iron deficiency is present, the RBCs might be hypochromic and microcytic.[16]

4.4 Differential diagnosis of PV: [17, 18]

- Secondary polycythemia due to hypoxia from obstructive sleep apnea, chronic lung disease, smoking, high altitude etc.
- Serum EPO level is elevated in secondary polycythemia but is low and occasionally normal in PV
- Essential thrombocythemia

- A positive CALR or MPL mutation and a normal erythropoietin, isolated thrombocytosis, absence of elevated hemoglobin concentration or red cell mass favor ET
- Chronic myelogenous leukemia (CML)
- Primary familial polycythemia due to mutations in EPO receptor and congenital secondary polycythemia due to mutations in globin genes, bisphosphoglycerate mutase, cytochrome b5 reductase-3.
- Specialized genetic tests will be positive for the particular congenital disorder present.

4.5 Treatment

Initially, the treatment depends on the risk stratification of the patient. The goals of current therapies in PV are to prevent the occurrence of thrombosis/vascular events; delay transformation to PMF or AML (Acute myeloid leukemia); reduce constitutional symptoms; maintain hematocrit <0.45 and manage special situations such as pregnancy or cardiovascular risk. Phlebotomies, aspirin therapy, interferon – α, hydroxyurea, Anagrelide, JAK 2 inhibitors like Ruxolitinib are some of the medications and treatments used.[7]

4.6 Prognosis

Currently, prognostication in PV relies on the European Leukemianet recommendations, International Prognostic Scoring system (IPSS) scores for overall survival.[6] With treatment, the median survival for most patients is 10-20 years. Major causes of death in untreated patients are thrombosis and hemorrhage. Fewer than 5% of patients develop acute myeloid leukemia, 10-15% of patients develop post-PV myelofibrosis at an average interval of 10 years from diagnosis. Most patients who develop myelofibrosis die within 3 years often from progressive bone marrow failure or further transformation to acute myeloid leukemia.[9]

5. Essential Thrombocythemia (ET)

Essential thrombocythemia is characterized by a sustained clonal proliferation of megakaryocytes in the bone marrow, with a peripheral blood platelet count greater than 450 x 10^9/L. [9]

5.1 Epidemiology

The disease is more common in females. The incidence of essential thrombocythemia increases with age, most patients present between the ages of 50 and 60.[19]

5.2 Pathophysiology

The proliferation of megakaryocytes is mainly due to clonal stem cells. Megakaryocyte progenitor cells in ET are hypersensitive to the action of cytokines like IL-3 (interleukin-3) and IL-6 (interleukin-6), and thrombopoietin leading to increased platelet production.[9] Mutations in the JAK2, MPL or CALR are seen in most cases. Increased platelet counts lead to increased thrombotic and hemorrhagic complications. High platelet counts (>1,000 x 10^9/L) are associated with acquired Von Willebrand disease resulting from the adsorption of Von Willebrand multimers onto platelet membranes. Qualitative abnormalities in the platelets themselves are also likely to contribute to the increased risk of thrombotic and hemorrhagic complications in ET.[9]

5.3 Signs and symptoms

Many patients are asymptomatic at presentation. Among symptomatic patients, common symptoms are migraines, headache, and dizziness. There can be various levels of thrombosis in major vessels and microvasculature including coronary vessels or deep vein thrombosis. The most common physical finding in ET is splenomegaly, which is mild when compared to other myeloproliferative neoplasms.[19]

Peripheral smears of patients with ET show platelet anisocytosis, ranging from very small to giant in size.[16]

5.4 Differential diagnosis

- Reactive thrombocytosis from chronic infectious or inflammatory causes like rheumatoid arthritis, tuberculosis etc. [20] In reactive thrombocytosis, platelet function is usually normal and the platelet count is usually < 1,000,000 × 10^9/L.[20]
- PMF

PMF includes large spleen, tear drop shaped red cells, leukoerythroblastic blood picture and collagen fibrosis on BM biopsy.[21]

- Myelodysplastic syndrome (MDS)

In MDS, bone marrow demonstrates dysplasia in a proportion of undifferentiated myeloblasts.[22]

5.5 Treatment

Treatment is based on risk stratification. The main goals in the treatment of ET include minimizing the risk for thrombosis as well as progression, normalizing peripheral blood counts, reducing constitutional symptoms, and managing special situations like pregnancy. Aspirin, Interferon – α, hydroxyurea, anegrelide, busalfan are some of the medications used.[7]

5.6 Prognosis

Currently, prognostication in ET relies on the European Leukemianet recommendations, International Prognostic Score for ET (IPSET) scores for thrombosis and survival.[6] ET is an indolent disease and has a good prognosis. With treatment, a life expectancy of 33 years is reported in ET in patients younger than 60 years. Compared to polycythemia vera, the life expectancy of patients with essential thrombocythemia is superior, [19] but a few patients with ET transform to acute myeloid leukemia (blast phase), and approximately 5% develop myelofibrosis.[9]

6. Primary Myelofibrosis (PMF)

PMF is a clonal hematopoietic stem cell expansion in the bone marrow, and it is accompanied by a reactive non clonal fibroblastic proliferation along with marrow fibrosis. As the bone marrow becomes fibrotic and normal hematopoiesis can no longer occur, extramedullary hematopoiesis (myeloid metaplasia) occurs in the liver and spleen.[9] Myelofibrosis can present de novo as primary myelofibrosis (PMF) or can be secondary to an antecedent myeloproliferative neoplasm namely, polycythemia vera (PV) or essential thrombocythemia (ET)[23]

6.1 Epidemiology

The disease is more common in Caucasians, with an equal likelihood of occurrence in both men and women.

The median age at diagnosis is 67 years.

Patients with PV and other MPNs can develop myelofibrosis late in their disease course.[9]

6.2 Pathophysiology

The clonal proliferation of hematopoietic stem cells produces growth factors like platelet-derived growth factor, transforming growth factor-B, epidermal growth factor, and basic fibroblastic growth factor which leads to fibrosis of the bone marrow. The bone marrow is hypercellular initially, but, as the bone marrow becomes fibrotic, normal hematopoiesis becomes diminished and patients become pancytopenic. This causes extramedullary hematopoiesis to occur in the liver and spleen causing these organs to enlarge.[9]

6.3 Signs and symptoms

PMF has a heterogeneous clinical presentation and up to 30% of patients are initially asymptomatic, but as the disease progresses, they become symptomatic. Decreased hematopoiesis and splenic sequestration leads to pancytopenia which may in turn cause fatigue, shortness of breath, hemorrhage and infections.[9] Bone marrow fibrosis and splenomegaly leads to abdominal symptoms and early satiety, constitutional symptoms such as weight loss, night sweats, and low-grade fever. Aquagenic pruritus, bone pain, and thrombosis are also seen.[7]

The peripheral smear of patients with PMF includes red blood cells of variable shape (like teardrop cells) and size, including variable degrees of polychromasia..[16]

6.4 Differential diagnosis [24]

- Essential thrombocythemia
- Chronic myelogenous leukemia
- Polycythemia vera
- AML or MDS with fibrosis

Fibrotic MDS is characterized by the presence of significant dysplasia, diagnostic chromosomal abnormalities, lack of splenomegaly, and absence of mutations that are characteristic for PMF. JAK2 mutations are found in MDS, in approximately 5% of cases.[25]

- Secondary marrow fibrosis from Infections, Autoimmune diseases, Chronic inflammatory conditions, lymphoid neoplasms, Metastatic malignancy, Chronic toxic myelopathies.[2]

6.5 Treatment

The choice of treatment is mainly guided by the symptom, feature or risk stratification. Currently, the therapies are primarily directed towards the treatment of anemia and other cytopenias, to manage symptomatic splenomegaly and constitutional symptoms, to improve quality of life, to improve survival and decrease the risk of transformation to acute leukemia. Another goal is to avoid thrombotic and bleeding complications. Erythropoietin, Danazol, Thalidomide, and Corticosteroids like Prednisone, Hydroxyurea, Ruxolitinib, Splenectomy, splenic irradiation and allogenic stem cell transplant are some of the treatment modalities used in this regard.[7]

6.6 Prognosis

Currently, prognostication in primary myelofibrosis (PMF) is calculated based on the International Prognostic Scoring System (IPSS), dynamic IPSS (DIPSS) and DIPSS-plus scoring.[26]

Patients asymptomatic at the time of diagnosis can have an indolent clinical course for several years. However, PMF has the worst prognosis among the MPNs, with a median survival of 3.5 to 5.5 years. Infection, cardiovascular disease, cerebrovascular disease, hemorrhage or thrombosis, and acute leukemia (blast-phase PMF) are the most common causes of death. It is very rare for patients with acute leukemia arising from PMF to achieve a remission from induction chemotherapy.[9]

7. Blast Transformation in Myeloproliferative Neoplasms: Secondary acute myeloid leukemia (AML) or blast-phase MPN (MPN-BP) [27]

The frequency of leukemic evolution varies depending on the MPN subtype. It is highest in PMF, with a risk of 10–20% at 10 years, followed by PV, with a risk of 2.3% at 10 years and 7.9% at 20 years. In ET, however, transformation to acute myeloid leukemia is considered relatively uncommon.[27]

Leukocytosis, exposure to myelosuppressive therapy, cytogenetic abnormalities, advanced age, and increased number of mutations in the genes associated with myeloid neoplasms are some of the factors that may be associated with leukemic transformation.[27]

The finding of 10–19% of blasts in the peripheral blood or in the bone marrow (BM), as well as the immunohistochemical detection of an increased number of CD34+ cells with cluster formation and/or an abnormal endosteal location in the BM, are indicators of an accelerated phase (AP) of the disease. The detection of more than 20% of blasts is diagnostic of blast phase.[27]

The prognosis of these patients is dismal, with a median overall survival ranging from 2.6–7.0 months. [27]

8. Oral manifestations in MPN

Myeloproliferative neoplasms have oral manifestations and although non-pathognomonic, their presence should alert the dentists and hematologists to avoid complications and to begin treatment at an early stage.[28]

Intraorally, PV and ET can manifest mucosal erythema, glossitis and edema with spontaneous gingival bleeding on occasions.[29] The lips and the cheek may also show purplish or red areas.[30] This increased tendency to oral bleeding predisposes to impaired oral hygiene and periodontitis and other dental infections.[1]

PMF can present with a similar picture and rarely extramedullary hematopoiesis in the mandible may occur.[31]These manifestations result from an increase in the number of circulating red blood cells, impaired blood flow and thrombocytopenia.[30]

In the blast phase MPN or AML, mucosal pallor due to anemia, spontaneous bleeding and petechial haemorrhages of gingivae, palate, tongue or lip as a result of thrombocytopenia, alveolar bone destruction, gingival hyperplasia due to leukaemic infiltration, numb chin syndrome and other neurologic manifestations andarthritic changes of TMJ are seen.[1,31]

Xerostomia may occur secondary to interferon use as a part of treatment.[30]

Implications for dental treatment: a medical consult and blood tests before any dental procedure are recommended to minimize risk of excessive bleeding and blood clots.[30]

Medical clearance is recommended for invasive dental procedures and such procedures are contraindicated in certain scenarios, such as when the patient is undergoing active chemotherapy or radiation therapy, patients with leucopenia, anemia and thrombocytopenia or if the patient has a splenectomy resulting in compromised immunity and thus is at increased risk of serious infections.[30]

Antibiotic prophylaxis may be required in some patients depending on blood indices (e.g., low neutrophil count), in patients with splenectomy with risk of immunosuppression, or in patients with in-dwelling central venous catheters.[30]

Elective oral procedures may be delayed in certain cases such as bone marrow transplantation and blood stem cell transplantation until the patient's immune system returns to normal which is about 6 to 12 months post- transplantation.[30]

Due to increased risk of excessive bleeding and thrombosis, intravenous and intramuscular sedation techniques as well as outpatient general anesthesia are to a certain extent contraindicated in these patients.[30]

In cases where patients are on low dose aspirin for treatment, non-steroidal anti-inflammatory medications like ibuprofen should be avoided for pain management or given after consultation with the oncologist. This is due to the risk of gastrointestinal ulceration and also due to its interference with aspirin's anti-clotting effect.[30]

Other measures to consider in preparation of the patient for routine dental surgery include obtaining better control of blood counts by phlebotomy or drug therapy and adjustment of any concomitant antiplatelet and/or anticoagulant therapy.[29]

Meticulous oral hygiene using soft bristle toothbrushes as well as topical antiseptics (chlorhexidine 0.12% mouth rinse twice a day) may be employed to manage gingival enlargement and if there is gingival bleeding, an antifibrinolytic mouth rinse may be added. [32]

9. Conclusions

Myeloproliferative neoplasms are rare malignant neoplasms with a significant risk profile. Recently, many advances have been made in the genetics, diagnostics and treatment modalities of these disorders. Although a rare occurrence, patients are sometimes asymptomatic or unaware of the disease. However, awareness of these diseases is important in order to help patients by looking at their history, clinical features, oral manifestations and blood counts. It is then possible to refer patients with a suspected case to hematologists and also to provide better dental treatment and care.

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