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Polycythemia Vera: A Malignancy in Hematology: Review Article

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ABSTRACT

Introduction: Myeloid neoplasm is a condition in which myeloid cells can undergo excessive clonal proliferation. One classification of the disease is polycythemia vera. Polycythemia Vera (PV) is a condition where there is an increase in the number of red blood cells reaching 125% of the calculation based on body mass and sex.
Content: This journal discusses polycythemia vera including the definition, epidemiology, etiopathogenesis, clinical manifestations, diagnosis, management and complications.
Result: Characteristics of diseases in obese patients at RSUD Dr. H. Chasan Boesoirie Ternate in 2019 were found to be 20-60 years 75 people (80%), women 69 people (72.6%), work as housewives 54 people (56.8%), the level of high school education was 36 people (37.9%), obesity I 68 people (71.6%), and the type of type 2 diabetes mellitus 46 people (48.4%).
Conclusion: PV is caused by mutations in the JAK2 gene. PV disease diagnosis based on the results of the history, physical examination and supporting examinations in the form of laboratory tests. PV disease can be managed with phlebotomy, administration of aspirin, and cytoreductive drugs. Patients with PV can survive more than 10 years if treated quickly and appropriately

Keywords: Neoplasm; myeloproliferative; polycythemia vera

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Introduction

An increase in the number of circulating red blood cells that persists for more than two months is considered polycythemia[1,2]. The syllable polycythemia when interpreted in Greek means poly (many), cyt (cells) and hemia (blood) [1]. The number of cases of polycythemia in general is quite large throughout the world.

In general, the classification of polycythemia is divided into two, namely polycythemia vera and secondary polycythemia. It is important to distinguish between the two diseases because often patients present with cardiovascular disease which is one of the earliest features of polycythemia, especially polycythemia vera[2]. In addition to the sake of diagnosis, the importance of distinguishing the two diseases is to determine the appropriate treatment given to patients with these diseases to reduce morbidity and mortality due to these diseases[2]. In this literature review, we will discuss about polycythemia from definition to proper management in dealing with polycythemia cases.

Definition

Polycythemia comes from the Greek words *poly* meaning many, *cyt* meaning cells, and *hemia* meaning blood. So polycythemia is a condition where there is an increase in the number of red blood cells reaching 125% of the calculation based on body mass and sex[1,2]. Polycythemia is also known as erythrocytosis which indicates a persistent increase in hematocrit levels > 2 months[3].

In general, polycythemia can be grouped into primary polycythemia or polycythemia vera and secondary polycythemia. Primary polycythemia or vera occurs due to excessive intrinsic activity in the bone marrow progressively and chronically because most of the erythrocyte population comes from an abnormal stem cell clone while secondary polycythemia occurs due to abnormalities in the bone marrow through increased erythropoietin due to certain factors[2].

Epidemiology

Globally, the incidence of primary polycythemia/vera (PV) is 1.9 per 100,000 people [3]. The incidences of PV are common in males and dominated by the age of 40-60 years. The annual incidence rate of PV is 2.3 per 100.000 population. The survival rate of PV without treatment is only 1.5 – 3 years while with treatment it can reach 10 years [1].

Etiopathogenesis

PV is a chronic myeloproliferation neoplasm with a negative Philadelphia chromosome that causes a clonal disorder of myeloproliferation in the spinal cord[4,5]. Myeloid cell proliferation is being replaced by an abnormal monoclonal proliferation process causing overproduction of red blood cell, platelet in essential thrombocytosis, and spinal cord fibrosis in primary myelofibrosis[6]. In 2005, researchers discovered a somatic mutation in the Janus kinase 2 (JAK2) gene. The JAK2 gene provides instructions for making proteins that play a role in cell proliferation[7]. This protein has an important role in controlling the production of erythrocytes, leukocytes, and platelets in hematopoietic stem cells in the bone marrow[8]. The JAK2 gene mutation most commonly associated with myeloproliferative neoplasms is located at exon 14 of JAK2. This mutation in exon 14 is called JAK2V617F[9]. JAK2V617F can be found in more than 90% of PV, as well as 50-60% in ET and PMF7. A small proportion of PV patients have a JAK2 mutation in exon 12[10]. The JAK2V617F mutation causes genetic instability in gene expression by triggering changes in chromatin structure and by reducing apoptotic responses to DNA damage[11]. The occurrence of mutations in JAK2 causes erythropoietin hypersensitivity which results in increased production of red blood cells[11]. Polycythemia vera naturally tends to progress to myelofibrosis, called post-polycythemia vera myelofibrosis (PPVMF)[12]. This transformation occurs in 25% of PV patients and decreases life expectancy[10]. There are no risk factors for the evolution of PV to PPV-MF. In PPV-MF, an increase in JAK2V617F was found as in PV, and CD34+ cells in peripheral blood[13].

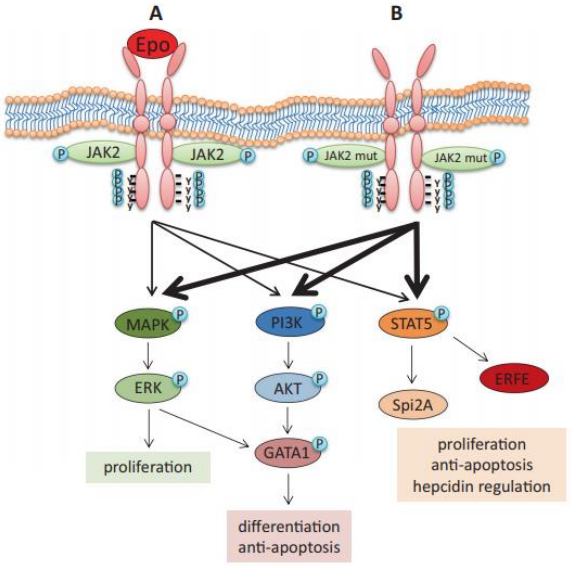

Figure 1. Mediated signaling *JAK2* [7].

Clinical Manifestation

Signs and symptoms of PV are divided into 3 phases, namely:

1. Early symptoms (*early symptoms*)

The initial symptoms of PV are minimal or even abnormalities are not always found even though it has been known through laboratory tests. The initial symptoms that occur are usually high blood pressure (72%), headache (48%), easy fatigue (47%), ringing in the ears (43%), itching (pruritus) (43%), visual disturbances (3l%), feeling sick. fever in the hands or feet (29%), memory impairment, difficulty breathing (26%), bone pain (26%), also bleeding from the nose, stomach (stomach ulcers) (24%).

2. Late symptoms*and*complications

As the disease progresses, patients with PV develop*hemorrhage*or thrombosis. Thrombosis is the most common cause of death from PV. Another complication is an increase in uric acid in the blood of about 10%, developing gout and an increased risk of peptic ulcer (10%).

3. Splenomegaly phase

About 30% of late symptoms progress to the splenomegaly phase. At this stage, bone marrow failure occurs and the patient becomes severely anemic, the need for transfusion increases, the liver and spleen are enlarged[1].

Diagnosis

The initial diagnosis is based on anamnesis, physical examination, and investigation[2].

1. History

In the history, it is necessary to know a history of tumor or malignancy, cardiovascular and cerebrovascular disorder, a family history of disease associated with myeloproliferative, neoplasms such as polycythemia vera, essential thrombocythemia, or primary myelofibrosis.

2. Physical Examination

On physical examination can be found splenomegaly and hepatomegaly, ruddy cyanosis (swelling of the mucosa and skin with cyanosis), conjunctiva plethora, and skin plethora (accumulation of fluid and blood in the conjunctiva and mucosa).

3. Support Inspection

Pemeriksaan pada polisitemia
Pemeriksaan Awal
Pemeriksaan hitung darah lengkap dan apusan darah tepi
Pemeriksaan zat besi/ ferritin
Mutasi JAK2
Konsentrasi EPO serum
Saturasi oksigen dan urinalisis (jika belum diperiksa sebelumnya)
Profil renal dan hepar (jika belum diperiksa sebelumnya)
Pemeriksaan Lanjutan
USG abdomen
Foto toraks
Pemeriksaan polisonografi (sleep test) atau fungsi paru
Aspirasi dan biopsy sumsum tulang
Mutasi JAK2 ekson 12
Pengukuran massa eritrosit
Analisis gen EPO reseptor
Analisis VHL

Figure 2. PV Support Inspection

Erythrocytes

To establish the diagnosis of polycythemia vera during the disease, an elevated erythrocyte mass must be demonstrated. The erythrocyte cell count is >6 million/ml in men and >5.5 million/ml in women, and erythrocyte smears are usually normochromic, normocytic unless iron deficiency is present. Poikilocytosis and anisocytosis suggest a transition to myeloid metaplasia late in the course of the disease.

Granulocytes

Granulocytes increase in number occurs in 2/3 cases of PV, ranging from 12-25 thousand/ml but can be up to 60 thousand/mL. In two-thirds of these cases there is also basophilia.

Platelets

Platelet counts usually range from 450-800 thousand/mL, even >1 million/ml. Often found with abnormal platelet morphology. d. B12 Serum B12 serum can be increased this is found in 35% of cases, and can also be decreased this is found in 30% of cases, and UB12BC levels are increased in >15% of cases of polycythemia vera

Bone Marrow

This examination is not necessary for diagnostics unless there is suspicion of other myeloproliferative diseases such as the presence of blast cells in the leukocyte count. Bone marrow cytology showed an increase in normoblastic cellularity in the form of trilinear hyperplasia of a series of erythrocytes, megakaryocytes, and myelocytes. Meanwhile, from the histopathology of the bone marrow, the presence of a pathological/abnormal morphological form of megakaryocytes and slight fibrosis is a pathognomonic sign of polycythemia vera.

Cytogenetic examination

In polycythemia vera patients who have not received P53 treatment or cytostatic chemotherapy, a karyotype can be found (see etiology). Variations of cytogenetic abnormalities can be found in addition to the above, especially if you have received P53 treatment or previous cytostatic chemotherapy[1].

Table 1. World Health Organization (WHO) Criteria for Diagnosis of Polycythemia Vera

Major Criteria	
Criteria 1	
Hemoglobin	Male: > 16.5 g/dl Female: > 16.0 g/dl
Hematocrit	Male: > 49% Female: > 48%
Red blood cell mass	An increase of 25% above average
Criteria 2	
Bone marrow morphology	Hypercellularity for age with panmyelosis, including prominent erythroid, granulocytic, and megakaryocyte proliferation with pleomorphic and mature megakaryocytes (different sizes)
Criteria 3	
*JAK2 V617F mutation*or	+
JAK2 exon 12 mutation	+
Minor Criteria	
Serum erythropoietin level	Subnormal

Table 2. International Working Group-Myeloproliferative Neoplasms Researchand Treatment (IWG-MRT) criteria for the diagnosis of secondary myelofibrosis

Major Criteria	
Criteria 1	
Documentation of previous diagnosis of polycythemia vera	+
Criteria 2	
Bone marrow morphology	Reticulin fibrosis grade 2/3 (0-3 scale), or reticulin fibrosis grade (on a 0-4 scale)
Minor Criteria	
Anemia* or not meeting requirements for phlebotomy and cytoreduction	There is
Leukoerythroblastosis	There is
Spleen size	Increased splenomegaly, defined as an increase in the size of the splenomegaly by 5 cm (calculated from the left costal arch) or newly palpated splenomegaly
Accompanying symptoms **	Consists of 1 of 3 symptoms

*Defined as hemoglobin value < 12 g/dL for female, and < 13.5 g/dL for male
* Weight loss of 10% for 6 months, cold sweats, and fever of unknown cause (temperature >37.5 C)

Management

Current PV therapy cannot prevent the natural evolution of diseases such as post-PV myelofibrosis, but it can reduce the risk of thromboembolism and bleeding. Initial therapy for PV was phlebotomy and aspirin administration to all patients, both male and female, regardless of risk factor classification. A phlebotomy is performed until the hematocrit is below 45%, and aspirin is given at a dose of 40-100 mg once a day. In low-risk PV patients with microvascular symptoms not controlled with once-daily aspirin, the aspirin dose is increased to twice daily[9].

High-risk patients can be given a cytoreductive drug such as hydroxyurea as a first line with an initial dose of 500 mg twice daily 15 in patients with a history of arterial thrombosis, aspirin is given twice daily. If a history of venous thrombosis is found, systemic anticoagulation should be added. If there is intolerance or resistance to hydroxyurea, second-line drugs should be considered, namely pegylated interferon, busulfan, and ruxolutinib [9]

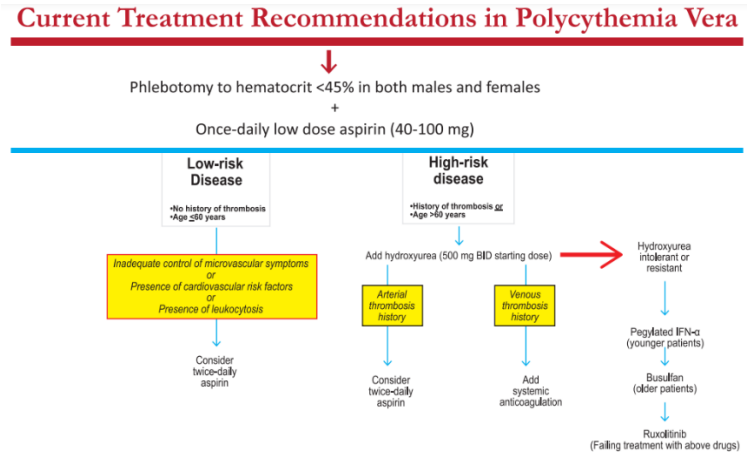

Figure 2. Recommendations for Management of Polycythemia Vera[9]

Complications

PV disease can cause various complications if not treated quickly and appropriately. Several complications that can occur, including thrombosis, bleeding, and transformation into leukemia. Thrombosis is the most frequent complication, which is 34-39%. Mutation *JAK2* causes activation and interaction of leukocytes and platelets that cause inflammation, causing vascular endothelial dysfunction[14].

While Erythrocytosis causes hyperviscosity of blood that triggers thrombosis. The stratification of risk factors for this disease aims to predict the occurrence of thrombotic complications. The risk assessment consisted of two categories: low risk without thrombocytosis (age <60 years without a history of

thrombosis, low risk with high platelets (>1,000 x 109/L). High risk, namely age >60 years with a history of thrombosis. High risk with PV refractory or intolerant to hydroxyurea[14]

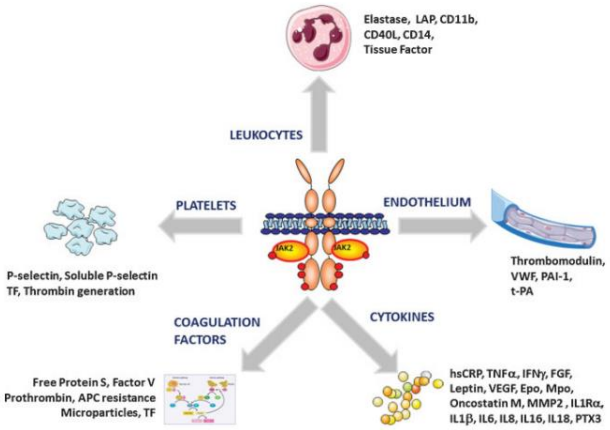

Figure 3: Effect of *JAK2*[14]

Prognosis

In general, PV patients have an average life expectancy of more than ten years in various studies, but it is hoped that the new decade would bring a greater life expectancy supported by the development of new medicines. Thrombosis is the most common cause of morbidity and mortality in cases of polycythemia vera, followed by myelofibrosis and the development of leukemia[15].

Conclusion

Polycythemia vera (PV) is a condition where the red blood cell count increases up to 125% of the calculation based on body mass and sex or a persistent increase in hematocrit > 2 months. The incidence of primary polycythemia/vera (PV) is 1.9 per 100,000 people. The etiology of PV is associated with a mutation in the JAK2 gene.

The diagnosis of PV can be made through history, physical examination, and investigations. There are two criteria that are used as a reference in establishing the diagnosis of PV, namely the WHO criteria and the IWG-MRT criteria. The principle of management of PV is to control the number of erythrocytes with initial therapy in the form of phlebotomy and administration of aspirin. Then individuals with high risk can be given hydroxyurea as the first line. Patients with PV can have a survival rate of more than 10 years if they receive appropriate treatment.

Conflict of Interest

There is no conflict of interest

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