

POLYCYTHEMIA VERA

A DISEASE OF A BONE MARROW CELL

What is polycythemia vera?

Polycythemia vera, often abbreviated as PV, is a disease that results from an abnormality of a very immature cell in the bone marrow, the site in which all blood cells are made. The altered cell develops a growth advantage and produces blood cells in such large numbers that they are overrepresented in the marrow. There is some variation in this abnormality. In virtually all cases of polycythemia vera, the marrow produces too many red blood cells. In many patients, the numbers of white blood cells and blood platelets are also elevated.

The increase in red cells and a reciprocal decrease in plasma can lead to blood that is thicker than normal (viscous) and does not flow normally.

What is the derivation of the term “polycythemia vera”?

The word “polycythemia” is composed of the Greek words “poly” (many), “cyt” (cells), and “hemia” (blood). Thus, it is applied to a disease in which there are too many of the principal cells (red, white, and platelets) in the blood. The term “vera” is from the Latin word meaning true. The latter term is used to distinguish this disorder from a host of other conditions that can result in an increase in the number of red cells in the blood.



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What are the symptoms and signs of polycythemia vera?

Polycythemia vera is detected in many patients when a periodic health examination uncovers an elevated red cell count. Patients usually experience only vague and non-specific symptoms. They may have had minor complaints, but none were sufficiently troubling to have led to a medical examination. The physician may discover an enlarged spleen through the physical examination or an imaging procedure of the abdomen. The disease also may be detected as a result of a medical examination for a blood clot.

Persons who have polycythemia vera may develop a ruddy complexion and have flushed palms, ear lobes, and cheeks as a result of the high concentration of the red colored hemoglobin in the blood. If their red cell count is very high and their circulation impaired by the thick, viscous blood, patients may have headaches, weakness, dizziness, ringing in their ears, or itching.

How is polycythemia vera diagnosed?

The disorder is diagnosed by the determination of the blood cell counts. A complete blood cell count (CBC) is a standard test that determines the concentration of red cells, white cells, and platelets in the blood and includes an examination of the blood cells stained with dye on a glass slide. The red cell count of a normal person is about 4.0 to 6.0 million cells per microliter of blood. (Men have higher normal values than women, on



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average about 5.2 million red cells in men and about 4.6 million in women.)

A person diagnosed with polycythemia vera has an increased number of red blood cells. The increase may be moderate or severe but usually will progress if treatment is not instituted.

Additional tests indicate the level of the red cells in the blood. The hematocrit is the percent of the blood that is composed of red cells. It averages 42 % in women and 47% in men. Hemoglobin is the compound in the red blood cell that carries oxygen. The hemoglobin concentration averages about 14 grams per 100 milliliters of blood in women and about 16 grams per 100 milliliters of blood in men.

In polycythemia vera, at the time of diagnosis, the hematocrit and hemoglobin concentration are increased in the same proportion as the red cell count. Thus, if the red cell count in a man with polycythemia is increased by 150 percent ($5.2 \times 1.5 = 7.8$ million cells per microliter of blood), the hematocrit ($47 \times 1.5 = 70$ percent) and hemoglobin concentration ($16 \times 1.5 = 24$ grams per 100 milliliters) will be increased by about the same proportion.

The white cell count is increased mildly in most patients. Examination of the blood slide aids in the diagnosis of polycythemia vera by showing an increase in neutrophils, a subtype of white cells. The increase is composed of mature functional white blood cells and usually does not progress.



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The platelet count is increased in many patients as well. The increase in platelets can worsen and cause patients to have an increased risk of blood clot formation that may require treatment.

The elevation of all the blood counts (polycythemia), is a very important clue that distinguishes the disease from other conditions resulting in increased red cell counts. In these cases, the white cell and platelet counts are usually normal.

In most cases of polycythemia vera, the diagnosis can be made from the physical findings and the blood cell counts. Several other tests may be helpful, including:

- measurement of the level of red cells in the circulation directly using a radioactive label attached to a sample of blood cells,
- measurement of the blood level of the hormone erythropoietin, and examination of the bone marrow. The erythropoietin level usually is very low in polycythemia vera and high normal or elevated in other causes of increased red cells. The marrow contains more than the normal number of cells as a result of the overexpansion of the blood-forming cells and is lacking iron, which has been used up making the additional red cells.



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What are the complications of polycythemia vera?

Patients commonly develop complications of polycythemia vera that result mainly from the increase in red cells and in platelets. At least three factors may contribute: too many red blood cells make it difficult for the blood to flow smoothly; too many platelets can lead to the formation of clots; and underlying vascular disease is commonly found in older persons with the disease. Perhaps as many as 50 percent of people with the disease develop complications resulting from clotting, either in veins or arteries. Clots in leg veins, liver veins, or lung veins can occur. Stroke, heart attack, or poor circulation to the feet and legs can result from blocked arteries to the brain, heart, or legs.

If the disease is untreated, there is a predisposition to have exaggerated bleeding at surgery. This effect appears to be related to the engorged blood volume in untreated patients. The excessive red blood cells, also, may block the ability of platelets to get to the injured blood vessel wall or may disturb clotting in other ways.

Itching of the skin can be troubling in some patients and this can be accentuated after warm showers or baths. The symptom is unpleasant, but not dangerous. This complaint often improves after treatment to decrease the red cell level in the blood.



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How common is polycythemia vera?

The disease principally affects adults over age 50, although it may occur very uncommonly in young adults. The incidence varies worldwide but probably is in the neighborhood of 1 case per 200,000 persons. It is somewhat more common in men than women and is more prevalent among Jews of European ancestry than other Europeans or Asians.

How does one get polycythemia vera?

An external cause of polycythemia vera has not been identified. The “cause” is known to be an acquired mutation, an abnormality of DNA that occurs in an early marrow cell. That abnormal stem cell is excessively active. It outstrips the millions of other similar cells in the marrow and produces all the blood cells in the patient. This single cell origin makes the disease a clonal disorder: all the cells are the offspring of the one mutant cell that will dominate blood cell production. The cells it makes are very similar to normal but they are made in excessive numbers. The DNA damage is not linked to any clear-cut environmental causes.

Other conditions can result in an increase in red cell numbers in the blood. These conditions arise as compensation for lower oxygen saturation of the blood (such as occurs at high altitude or with certain heart and lung diseases that prevent normal oxygen transport by the blood), or from an inappropriate increase in secretion of erythropoietin (a hormone made in the kidney and released into the blood), which stimulates red cell production in the marrow.



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How is a person with polycythemia vera treated?

The therapy for polycythemia vera takes into consideration three principal factors: the manifestations and rate of progression of the disease, the patient's age, and concurrent chronic diseases. The objective of treatment is to decrease the number of red cells to normal or near normal levels. If the platelet count is high or becomes high over time, that change may require treatment as well.

Phlebotomy. Phlebotomy, or the removal of blood from a vein in a manner similar to a blood donation, is the usual starting point of treatment. A volume of blood is drawn at regular intervals, decreasing the number of red blood cells and trying to aim for normal red cell counts during a period of weeks to months. Phlebotomy can be the sole form of treatment required for many patients, sometimes for many years. The disease may be controlled with withdrawal of a volume of blood every few months.

Drug Therapy. Aspirin is sometimes prescribed to help reduce the risk of blood clots. The drug acts on the platelets to decrease their tendency to form clots.

Anagrelide is another drug that can be used if platelet numbers are too high. The drug can blunt the rate of platelet formation in the marrow.

In some patients, phlebotomy alone cannot keep up with the overproduction of red cells and can accentuate



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the overproduction of platelets, worsening the latter problem. If that circumstance occurs, use of drugs to suppress the marrow production of red cells and platelets may be used with or without phlebotomy. Many chemotherapy agents have been used to treat polycythemia vera. The most commonly used is hydroxyurea, which is a pill and thus relatively easy to use. It has few side effects, and helps to reduce both the red cell and platelet counts.

Radiotherapy. Radiotherapy in the form of radioactive phosphorus (^{32}P) given as sodium phosphate in liquid form by mouth can be a useful treatment in some older individuals. One or two treatments may decrease red cell and platelet production, lessening the need for phlebotomy or chemotherapy for long periods.

Interferon and other chemotherapy agents are available in special cases but are not used in most patients either because they are not as effective, are inconvenient to administer, or may have more adverse effects than benefits.

How successful are the treatments for polycythemia vera?

Persons with polycythemia vera who are treated appropriately have virtually a normal life expectancy. The disease usually does not interfere significantly with everyday activity and employment. Patients may, however, sometimes have disability from clots or



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troublesome symptoms. These should be minimized with careful medical supervision and therapy to keep the red blood count near normal. Several studies have shown that there is an increased risk of developing acute myelogenous leukemia after the use of some chemotherapy agents and radioactive phosphorous, if used repeatedly. In many patients, these approaches can be avoided; in others, they are needed to control the disease and can be beneficial.

What is the spent phase of polycythemia vera?

In some patients after years or decades of disease, the disturbed marrow cell that produces the disease undergoes further mutations and behaves quite differently. It no longer overproduces red cells. For a time, the red cell count may stay near normal without treatment or drop below normal, resulting in anemia. The spleen may enlarge, sometimes to a troublesome size, and the marrow may produce fibrous or scar tissue that reduces its ability to make red cells and platelets. The platelet count may fall to low levels. Immature white cells may be released from the marrow into the blood. The approach to therapy at this time should be individualized to meet the problems at hand. Transfusion of red cells may be required. In some cases, the low red cell count, low platelet count, and massive enlargement of the spleen may require splenectomy. Treatment decisions require synthesizing many factors before recommendations are presented.



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Where can I get more information about polycythemia vera?

Consult your physician or a hematologist (a physician who specializes in blood disorders). You can also contact The Leukemia & Lymphoma Society at 1-800-955-4572 or visit The Society's web site at www.leukemia-lymphoma.org

A web site that discusses polycythemia vera is sponsored by the Association of Cancer Online Resources at www.acor.org/diseases/hematology/mpd

Short Glossary

Erythrocytosis: An increase in red blood cell (erythrocyte) level from any cause.

Myeloproliferative disorders: A term that had been used to show the similarity in origin of polycythemia vera, essential thrombocythemia, chronic myelogenous leukemia, and idiopathic myelofibrosis (formerly agnogenic myeloid metaplasia) before it was appreciated that they are linked together by being clonal diseases that originate in a primitive marrow cell. The



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affected primitive marrow cell normally makes red cells, white cells, and platelets. This cell of origin accounts for all three cell types being affected in these diseases. Another similar feature is that each results in the overproduction of mature, functional blood cells.

Phlebotomy:

The removal of blood from a vein to obtain small amounts of blood for diagnostic testing or larger amounts of blood from a transfusion donor. The technique is also used to treat two diseases: polycythemia vera, in which there is an overabundance of red cells in the blood, and hemochromatosis, a disease of iron overload. In the latter case, phlebotomy is a means of removing large quantities of iron contained in red cells. This treatment will ultimately decrease the iron in tissues.



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Platelets (synonym: thrombocytes):

Blood cells that help prevent bleeding by causing clots to form at the site of a blood-vessel injury. In polycythemia vera and essential thrombocythemia, the increased numbers of platelets play a role in the high risk of thrombosis in these diseases.

Red Cells (synonym: erythrocytes):

Blood cells that pick up oxygen as they circulate through the lung and unload oxygen to all tissues as they flow through tissue capillaries.

Red Cell Mass:

The total mass of red cells in the entire circulation. For example, a medium-sized person may have a total blood volume of 5000 milliliters of which 2250 milliliters are red cells and 2750 milliliters are plasma. The total body hematocrit (red cell volume) would be 2250 divided by 5000 or 45 percent.

Thrombocytosis:

An increase in blood platelet (thrombocyte) level from any cause.



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White Cells (synonym: leukocytes):

Blood cells of three major types: granulocytes, monocytes, and lymphocytes. Virtually all the white cells play a role in the defense against infection. Like other blood cells, they are formed in the marrow and enter the blood, but unlike red cells and platelets, they migrate from the blood into the tissues.

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