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Polycythemia rubra vera : co-related case reviews

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Polycythemia rubra vera

Corellated Case Reviews

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The history of polycythemia rubra vera dates back to 1892 at which time a European physician named Vaquez was treating a patient in whom he had diagnosed congenital heart disease. This patient was plethoric and cyanotic but without any ausculatory findings. When the patient died a year later, a post-mortem examination revealed a normal heart. Vaquez was then the first man to describe the disease entity which another physician named Osler later defined in 1903. This disease was known by the names of its discoverers for many years thereafter.

Other accepted, synonomous titles are erythremia, myelopathic polycythemia, erythocytosis megalosplenica, and cytogenic polycythemia. The most common reference name is primary polycythemia which descriptively differentiates this disease from a secondary form of polycythemia, or erythrocytosis, which refers to an increase in the number of erythrocytes as a result of some primary disease resulting in pulmonary or cardiac embarrassment with the subsequent need for more oxygen-carrying tissue. Also to be differentiated is relative polycythemia which is the result of a deficit in plasma volume and a misleading elevation of the hamatocrit.

Polycythemia refers to an increase in the hemoglobin concentration or an increase in red blood cell mass. Primary polycythemia is a chronic disease of unknown etiology and characterized

by hyperplasia of all the cellular elements of the bone marrow. Although one's lifespan may be greatly increased with treatment, the disease is uniformly fatal and without a single reported case of spontaneous recovery. (1)

Primary polycythemia is very infrequently found in the non-white races, however; all patients in this series are Caucasion. The incidence is high among Jewish people. Men are affected slightly more frequently than women, the 53.3 per cent male incidence being compatible with a reported 1.3:1 ratio of men to women. (2) From seven to ten per cent of the cases have been reported to be familial, and in these cases the disease is seen in children. However, in children the disease is atypical by being asymptomatic and without a left shift in the neutrophilic series or a granulocytosis. (3) Diagnosis is usually made during the fifth decade of life, and symptoms can usually be traced approximately five years prior to the time of diagnosis.

Although no one claims to know the etiology of the disease, several theoretical concepts have been proposed in an effort to explain its pathogenesis.

A very interesting question is why does plethora, a constant finding in this disorder and a phenomenon which inhibits red cell formation in otherwise normal men, fail to check and inhibit its own development in polycythemia vera? Some feel that with the

complete answer to this question will come the answer to the pathogenesis of this disease process. (4)

Gurney and others propose that if erythropoietin regulates erythropoiesis, then the status of erythropoietin in polycythemia vera assumes the greatest importance. This proposal considers the following mechanisms: With the normal red cell, the organ of production makes erythropoietin. This erythropoietin in turn regulates production of red cells by the marrow. The red cells act upon the organ of production, reducing production. With this in mind, one may consider four explanations for polycythemia vera.

1. An abnormal red cell may be interpreted by the organ of production as a decrease in the number of red cells.

2. An abnormal organ of production which is insensitive to the plethora resulting from increased erythropoietin elaboration goes unchecked and continues excessive erythropoietin production.

3. An ectopic production of erythropoietin may coexist with a normal organ of production. The resulting plethora may stop erythropoietin production in the normal organ of production but not affect the ectopic site.

4. Abnormal marrow may produce red cells in the absence of erythropoietin. (5)

According to this scheme, the plethora in polycythemia vera is either a consequence of an excess of erythropoietin as in 1,

2, and 3; or is produced in the absence of erythropoietin as in 4.

Another concept which is frequently mentioned is that of marrow hypoxia. This suggests that the arterioles of the bone marrow become constricted and thereby act as a stimulus to erythropoiesis. Portal thrombosis has been considered as a cause of primary polycythemia. Yet another theory is the antithesis of pernicious anemia which embodies the concept of an excessive gastric hematopoietic factor. (6)

The peripheral blood smear in this disease is often highly suggestive and has frequently been the evidence on which an asymptomatic case has been referred for further diagnostic proceures.

The red blood cell count is usually between seven and ten million per cubic millimeter. The cells may show slight anisocytosis, but they frequently appear normal. Miale states that polycythemic levels certainly exist if the red cell count is greater than 5.7 million in women or 6.4 million in men. (2) In this series, the presenting red cell values at the time of diagnosis ranged from 6.1 million to 10.78 million.

An elevated packed cell volume is always present in the untreated patient during the erythremic phase. It is this abnormality that is primarily responsible for the increased viscosity which may be two times normal. The highest hematocrit ever re-

corded was 92 per cent with a red cell count of 10.37 million. (2) In our series, hematocrit values ranged from fifty to seventy-seven per cent. Because of variations in plasma volume, the packed cell volume does not always or exactly follow the red cell count. A corellation certainly does exist, however.

Percentage values for reticulocytes are not significantly increased in primary polycythemia unless one is hemorrhaging, in which case there would be a resemblence to a hypochromic, microcytic anemia. Absolute reticulocyte counts are always elevated.

The hemoglobin content of the red cell varies, and an increase in the number of red cells does not always mean a proportionate increase in grams per cent because of decreased mean corpuscular volume and mean corpuscular hemoglobin. In this series, the hemoglobin values fell within the generally reported range of eighteen to twenty-four grams per cent, except in the presence of severe hemorrhage or terminal stages of myelofibrosis or leukemia.

The mean corpuscular hemoglobin is usually normal but may be low following venesection. The mean corpuscular volume and mean corpuscular hemoglobin concentration may be either normal or low depending upon the treatment being utilized and the status of the disease. Very high red cell counts are usually accompanied by a low mean corpuscular volume.

A very definite correlation exists between the elevation of the hematocrit, with its subsequent increase in viscosity, and the circulation time. Our reported circulation times, using the arm to tongue method, were between eighteen and twenty-two seconds.

Sedimentation rates are characteristically delayed.

The usual primary polycythemic leukocyte count is between ten and fifty thousand per cubic millimeter. A peripheral smear typically demonstrates a left shift, and one may find metamyelocytes and myelocytes. (3) As expected with pan-hyperplasia of the marrow, leukocytosis varies proportionally with erythrocytosis. And, because this is a myeloproliferative disease, the leukocytosis and left shift are a function of the marrow produced granulocytic series. In this series, white cell counts ranged from nine to twenty-two thousand per cubic millimeter. In untreated patients the white count was usually found to be greater than fifteen thousand, and the left shift was variable. Promyelocytes were seen in the peripheral smears of a few patients, juvenile neutrophiles in numbers greater than one per cent were observed in several patients, and band forms greater than twenty per cent were frequently present.

Wintrobe reports that twenty per cent of patients presenting with primary polycythemia will have normal platelet counts (6); however, our series reveals only ten per cent with normal plate-

let counts at the time of diagnosis. The lowest observed platelet count was 442,000 per cubic millimeter. Conversely, the highest count was 1.96 million per cubic millimeter at the time of diagnosis.

Eighty per cent of the calculated plasma volumes in this series were well within the normal limits. Interestingly, two patients had increased plasma volumes. One was eight and the other thirteen cubic centimeters above the upper limits of normal. Both of these, however, were accompanied by markedly increased total blood and red cell volumes.

One hundred per cent of the red cell volumes were increased. These ranged from three to eighty-one cubic centimeters per kilogram above the upper limit of normal with an average increase of twenty-seven cubic centimeters per kilogram above the normal limit.

As one would expect, one-hundred per cent of the total blood volume calculations were elevated. These ranged from two to ninty-four cubic centimeters per kilogram above normal with an average increase of thirty cubic centimeters per kilogram above the upper limit of normal.

In a series reported by Wintrobe, primary polycythemic patients usually had a red cell volume between 38.8 and 93.9 cubic centimeters per kilogram. These are well over his stated normal of 29.9 cubic centimeters per kilogram and compare favorably with

our series. (6)

The classic bone marrow of polycythemia vera demonstrates hyperplasia of all cellular elements. All marrow, including that of the extremities, becomes hyperplastic with the result that little fatty marrow remains. The percentile values for the different cell types are not strikingly different from normal because they are partially preserved by pan-hyperplasia. (2,6) The normal myeloid:erythroid ratio is in a range from six:one to two:one. Any ratio smaller than two:one may be considered indicative of erythrocytic hyperplasia. (7)

In primary polycythemia the usual marrow demonstrates moderate to marked hypercellularity with a marked decrease in the myeloid:erythroid ratio. In our series no ratio was greater than five:one, most were below two:one, and the smallest was one:three. Erythropoiesis is usually markedly increased, normoblastic, and iron deficient. Iron stores are decreased. The megakaryocytes are moderately to markedly increased. Granulopoiesis is increased but to a lesser degree than is erythropoiesis. Plasma cells and reticuloendothelial elements are normal.

Although the spleen is usually enlarged, it is not the site of blood formation in uncomplicated polycythemia vera. Although erythropoiesis is usual, megakaryocytosis may frequently be a striking feature. Marrow smears or sections from primary poly-

cythemic patients are reportedly frequently difficult to distinguish from those of chronic granulocytic leukemia and essential thrombocytosis. This difficulty may be overcome occasionally by considering them as three variants of the myeloproliferative syndrome. (8)

Ventilation and oxygenation as well as pulmonary diffusing capacity have always been assumed to be normal in polycythemia vera. Recently, however, an increased pulmonary diffusing capacity has been reported with the claim that pulmonary capillary blood volume is reduced as the possible consequence of widespread thromsis in small pulmonary arteries. From this comes the interesting speculation that some patients may have impaired gas exchange which could lead to a degree of secondary polycythemia superimposed upon the primary disease. (9) Arterial oxygen saturations in this series were within normal limits with values from ninty-two to ninty-nine per cent. Although this disease is not associated with significant reductions in arterial oxygen saturation, the arterial oxygen tension, which is stated to be a more sensitive index of hypoxia, has been found to be below normal in some patients. (10)

The causes responsible for the bleeding tendency in polycythemia vera are not agreed upon by the authorities in the field of coagulation, yet it is stated that a reasonable conclusion is

the qualitative platelet defects and relative fibrinogenopenia---the result of a decreased amount of plasma per volume of blood---are the most common causes for the hemorrhagic diathesis. (11) Reinhard reports a coagulation defect in the abnormality of thromboplastin regeneration and reduced activity of platelet factor 3 in primary polycythemic patients with thrombocytosis. (3) Poor clot retraction is well known, and fibrinolysis has been reported. The two accelerator factors, factor V (proaccelerin) and factor VII (proconvertin), have been described as reduced in this disease. These factors are primarily concerned with the conversion of prothrombin to thrombin in the second stage of clotting. Variable bleeding times are associated with deficiencies of the accelerator factors, yet bleeding and coagulation times are usually normal in polycythemia vera. Prothrombin, factor II, deficiencies have been reported, and this is supported by our series. Factor X, the Stuart-Prower factor which is involved in the first stage of clotting, has likewise been described as deficient in this disease. (12, 13)

Slight increases may be found in serum bilirubin, urine urobilinogen and stool urobilin, however, values recorded in this series were normal. Plasma from polycythemic patients has been shown to be hemolytic to normal red cells. (6)

Several plasma abnormalities have been reported in associ-

ation with polycythemia vera. Serum acid beta-glycerophosphatase and beta-1- and gamma-globulins may occasionally be elevated, but other serum enzymes and plasma amino acids are normal.. The elevated blood histamine levels are felt to be the result of increased numbers of circulating basophils. Plasma vitamin B_{12} levels, characteristically elevated in chronic granulocytic leukemia, are also high in some cases of polycythemia vera. (14)

Hyperuricemia, leading to a secondary form of gout, is found in seven to ten per cent of patients according to most series reported. By accepting as elevated all values over six milligrams per cent, this series claims a twenty per cent incidence. The highest value was 11.5 milligrams per cent in a man admitted for ureteral colic and who died two months later from uremia secondary to malignant hypertension.

The disturbance of uric acid metabolism in gout is attributable to increased metabolism of nucleic acids in the hematopoietic tissues with elaboration of intermediate products of purine metabolism. This form of secondary gout may be differentiated from primary gout by observing the rapid peak of isotope incorporation into uric acid in primary gout. (6, 15)

Chromosome studies represent a relatively new and unexplored diagnostic technique in the field of myeloproliferative diseases. In chronic granulocytic leukemia, one usually can

demonstrate a low leukocyte alkaline phosphatase and the presence of the Philadelphia chromosome. The converse is usually true of primary polycythemia. However, these enzyme levels may be normal in both diseases. Chromosome studies have not had sufficient trials to verify their use. (16)

Keeping in mind the facts and concepts presented in the previous pages, one can more readily understand the signs and symptoms attendant in this still unexplained disease.

The classical diagnostic triad is a relatively constant finding. Rubor of the face, hands and feet is almost uniformly present, but it is seldom the patient's chief complaint. Splenomegaly is generally considered to be present in seventy-five per cent of the cases. Over eighty per cent of this series had splenomegaly, and twenty per cent complained of left upper quadrant pain. The third and always present finding is an elevation of the red cell mass.

Patients suffering from this disease develop most of their symptoms as a result of the increase in blood viscosity. The variety of complaints with which these patients present may be so great that often a psychoneurotic disorder is thought to be their main problem. (17) Headache is the most common neurological complaint; but also common are dizziness, paresthesias, and visual disturbances. Generalized or lower extremity weakness and leg

pain are very frequent chief complaints. Less common presenting symptoms include tinnitis, syncope, siezures, renal colic, hematuria, hemorrhage, and dyspnea. One author reports a ten per cent incidence of pruritis and describes it as one of the most intolerable and refractory symptoms, and a twenty per cent incidence of skin lesions due to small capillary thromboses. (1)

The physical findings generally parallel the duration of the disease and the status of the bone marrow and peripheral blood. Another factor is the response to treatment, if initiated. The abnormal bone marrows were almost always compatible with the diagnosis of polycythemia vera. Hepatomegaly was slightly more common in this series than in a larger series which reported a fifty per cent incidence. The incidence of hypertension in our series was forty-five per cent. All except two of the hypertensive patients had both systolic and diastolic pressures in excess of 140 over 90 millimeters of mercury, respectively. This same incidence was observed in the larger group (3) and a group observed by Wintrobe. However, the criteria for the latter group consisted only of a systolic pressure greater than 140 millimeters of mercury.

Cardiomegaly, most commonly present as left ventricular hypertrophy, nearly approached a fifty per cent incidence in this series. Previous myocardial infarction was diagnosed in ten per cent, and one case of pulmonary infarction was reported in this

series. Radiographic evidence of increased pulmonary vasculature was commonly reported in our patients. Also common were varices, especially in the lower extremities, with an incidence certainly greater than in a random population. Cerebral thrombosis and even superior vena caval obstrucion occurred within this series. Understandably, thrombosis is the most common and serious complication, especially a vascular lesion in the brain. Miale reports his percentages as follow: Thrombophlebitis (leg or arm), thirteen per cent; Cerebral thrombosis, ten per cent; Coronary thrombosis, four per cent; and, Other, four per cent.

The incidence of duodenal ulcers in our series was ten per cent, and this corellated with Wintrobe's eight to sixteen per cent.

Two syndromes have been associated with primary polycythemia. Gaisboch's syndrome is the occurance of polycythemia vera and hypertension in the absence of splenomegaly. The other, Mosse's syndrome, implies the presence of polycythemia vera in conjunction with hepatic cirrhosis. Most authorities today feel that when these combinations of findings are observed, they merely represent a transient form of the disease and will eventually demonstrate the other characteristics typical of primary polycythemia.

Cirrhosis of the liver and occlusion of the hepatic veins, the Budd-Chiari syndrome, reportedly occurs very infrequently as

part of polycythemia vera. (3) The frequency with which polycythemia vera terminates in myelofibrosis and the speculation that DiGuglielmo's disease can be considered a malignant form of polycythemia vera, have led to their inclusion within the confines of this syndrome. (18)

Since no cure exists, the aim of treatment in polycythemia vera is to attain and maintain, as nearly as possible, a normal blood volume, viscosity and thrombocyte level.

The earlier treatment is instituted, the longer the survival time. As previously stated, diagnosis is usually made during the fifth decade of life; and symptoms can usually be traced approximately five years prior to the time of diagnosis. In the group of patients from our series who are known to be dead, the life-span following diagnosis ranged from five to twenty years with an average survival time of 11.2 years. If one assumes that each patient had developed his disease five years prior to diagnosis, then the maximum average survival time would be 16.2 years. in this treated group. A more realistic survival time would be one between 11.2 and 16.2 years, the average being 13.7 years. If, however, symptoms can more often than not be traced to five years prior to diagnosis, the average survival time would be somewhat in excess of 13.7 years. The significance of this value will be explained later.

According to life expectancy tables published by the National Office of Vital Statistics in 1957, life expectancy at age forty is 33.4 years and at age fifty it is 24.8 years. Therefore, the typical primary polycythemic patient who presents during the fifth decade and has a survival time of 13.7 years will be victim of death which is premature by 11.1 to 19.7 years.

Therapy of polycythemia vera consists of judicious use of phlebotomy, chemotherapy, and/or radiophosphorus.

During the onset phase when the patient is asymptomatic, treatment should be conservative and preventive to avoid damage to the reticulo-endothelial system. No blood should be withdrawn at this stage because it is the most potent stimulus for erythropoiesis. The patient should be instructed to consume an iron poor diet and return for follow-up every six months in an effort to detect early the erythremic phase.

Although bleeding is the treatment of choice during the erythremic phase, it results in several unwanted side effects. In addition to stimulating red cell formation, it causes hypoproteinemia, hypochromic polycythemia, increased thrombocytopoiesis with subsequent thrombosis, circulatory collapse in older people with rigid vessels, and thrombosis in arm veins. (1) Certainly the plethora should be relieved in all instances. A theoretical account of the danger of plethora is appreciated from the depend-

ence of blood viscosity on hematocrit. (19) Blood is withdrawn when the hematocrit reaches fifty-five per cent. Adjunctive myelosuppressive therapy is used when, to keep the hematocrit below fifty-five per cent, it is necessary to withdraw blood so frequently that iron deficiency anemia results; and if platelets rise significantly above normal. The amount of blood withdrawn varies with each patient and requires the use of serial hematocrits to ascertain the resulting status. Several patients with hematocrits between seventy and seventy-five per cent required the withdrawl of between two and four thousand milliliters of blood, at a rate not exceeding one pint per day, to obtain a satisfactory hematocrit in the fifties. Maintenence use of phlebotomy is then reduced to a usual rate of one pint over a number of weeks, varying with the refractiveness of the disease and in conjunction with the chemotherapeutic agent used, until a desired remission is obtained.

The nitrogen mustards and related alkylating agents are highly reactive and toxic drugs. They have also been referred to as nucleotoxic and radiomimetic agents. It is believed that they combine primarily with the phosphate groups in deoxyribonucleic acid to inhibit rapidly growing cells. Their effect on nucleic acids is suggested by their ability to induce mutations and to cause the formation of tumors in mice. The newer alkylating

agents such as triethylenemelamine (TEM) have the advantage of being better tolerated orally than is nitrogen mustard. However, all alkylating agents can produce severe bone marrow depression with thrombocytopenia as a frequent complication. (20) The therapeutic dose of TEM must be determined individually for each patient. Either 2.5 or five milligram tablets are administered every one to three days to a total dose of usually fifteen to forty milligrams. Remissions lasting many months were frequently observed. In other patients, small maintenance doses were required every few weeks and usually in conjunction with phlebotomy.

Radiophosphorous, introduced in 1940, has been considered an inexpensive, safe, and, when combined with phlebotomy, highly effective treatment. It nearly doubled the life span after diagnosis in comparison to the duration of the illness prior to the use of phosphorous. Unfortunately, the occurrence of myelofibrosis and leukemia as late complications in the course of polycythemia vera is being recognized with increasing frequency. This terminal leukemia is usually of the myeloid type and follows an acute or chronic course. Varying reports on the terminal stage of polycythemia vera being leukemia leave much doubt as to whether the cause could be radiophosphorus therapy. Several reporters have seen a terminal leukemia in patients treated with phlebotomy alone. Many feel it is merely the result of allowing patients to live

long enough to develop the disease. Furthermore, even before radiophosphorus is administered, some investigators find it possible to segregate a high-risk leukemia group on the basis of higher white counts, greater incidence of splenomegaly, and greater frequency immature white cells in the peripheral blood. (21)

In a series recently reviewed by Modan, acute leukemia appeared as the terminal disease following polycythemia vera in eleven per cent of patients treated with radioactivephosphorus, 8.9 per cent of those receiving x-ray therapy, and less than one per cent of the non-radiated. Furthermore, he stated that the risk of developing acute leukemia is dose dependent following radiation, and an increased risk does not follow a prolonged survival. He cited two other series. One by Perkins consisted of 127 polycythemia vera patients treated without radiation. No case of leukemia was observed, and the median length of survival was 13.6 years. The other, by Lawrence, utilized radioactivephosphorus for treatment. No statement of leukemia incidence was made, but the median length of survival was 13.2 years. (22)

In our series and the series reviewed by Perkins, both of which utilized chemotherapy primarily, survival times were slightly greater, 13.7 and 13.6 years respectively, than in the series by Lawrence which utilized radiophosphorus and claimed a survival

time of 13.2 years.

Treatment in the terminal phase is primarily supportive with some variation in therapeutic agent depending on the terminal outcome of the disease. Erythropoietic deficiencies occur and lead to aplasia or fibrosis. Leukopoietic deficiencies may result in leukemia or myeloid metaplasia. Thrombocytopoietic deficiency causes thrombocytopenia or megakaryocytic leukemia. Plasmacytopoietic deficiencies may result in multiple myeloma. In these situations the supportive treatment consists of transfusions, corticosteroids and vitamins. (1)

An interesting paradox is that late in the course of polycythemia vera, when extensive myelofibrosis has taken place, it is often necessary to treat with blood transfusions. Splenic irradiation may be utilized if this organ becomes uncomfortably large. However, splenectomy is contraindicated because it results in an increase in platelet count and subsequent fatal thrombosis.

SUMMARY

1. In all series, the incidence of primary polycythemia is greatest in white, non-jewish males in the fifth decade of life.

2. Although many theoretical concepts have been proposed, the etiology and pathogenesis still remain unknown.

3. The peripheral blood picture always reveals an elevated packed cell volume and usually demonstrates a left shift in the presence of leukocytosis.

4. Plasma volumes are frequently decreased; however, this occurred less frequently in our series than in others reported. Red cell volumes and total blood volumes were consistently elevated.

5. A bone marrow compatible with the diagnosis of polycythemia vera is almost always demonstrable at the time of diagnosis.

6. Although the spleen is not the site of blood formation in uncomplicated polycythemia vera, it is usually enlarged.

7. Arterial oxygen saturations were consistently normal. Arterial oxygen tensions, however, have been reported as decreased.

8. Numerous plasma abnormalities have been reported, but the causes responsible for the bleeding tendency in this disease remain unidentified with certainty.

9. Uricemia was seen twice as frequently in our series than in others reported.

10. Leukocyte alkaline phosphatase is usually increased in primary polycythemia.

11. The numerous symptoms of this disorder are primarily related to the increased blood viscosity.

12. Classical signs of primary polycythemia are rubor, splenomegaly and an increased red cell mass. Hepatomegaly was more frequently observed in our group of patients than in others.

13. Of greatest interest is the increased length of survival time observed in this series of patients as compared to other series. This is contributed to the judicious use of phlebotomy and triethylenemelamine in conjunction with close observation by a most competent physician.

14. The occurrence of leukemia as a terminal complication of polycythemia vera is markedly decreased when radiation therapy is not utilized.

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