POLYCYTHEMIA RUBRA VERA

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SUMMARY

This study spreading over years 1989 to 1996, was conducted at Hayat Shaheed Teaching Hospital and includes fifteen selected cases of Polycythemia Rubra Vera (PV). The most incident age was 65 years; male 13 were more affected than females. Common symptoms were pruritis, heartburn, dizziness, headache and vertigo. Common signs were generalized plethora, splenomegaly, dilated and engorged retinal veins and hypertension. The most sensitive tests were raised hemoglobin (Hb%), red blood cell (RBC) count, and panmyelosis (i.e, raised RBC count, TLC and platelet count) with characteristically low ESR (0-3). Specific tests included raised red cell mass (26-34 ml/kg for male and 21-29 ml/kg in female) and normal P02 (>92%). Phlebotomy was the initial treatment to control the symptoms of hyperviscosity and the response was dramatic. However long-term management included ^{32}p for those above 60 years and Hydrea for the young (i.e, below 60 years). Two patients were lost to the follow up; rest of the 13 patients are still alive and in reasonably good control and come for regular follow ups. There have been no complications.

INTRODUCTION

Polycythemia Rubra Vera (PV) is a relatively common disease and is characterized by both clinical and laboratory criteria. Clinically plethora, splenomegaly (75%), and hypertension are cardinal signs alongwith engorgement of retinal veins. Headache, prutitis, dizziness, vertigo, joint pains, epigastric discomfort and dyspepsia are common symptoms as are strokes and failing vision in one or both eyes.

Laboratory criteria include features of panmyelosis i.e, raised HB% (19G%), high PCV (>68%), increased TLC and platelet count, with a characteristically low ESR (0-3 mm Ist hour) and high red cell mass. However causes of secondary polycythemia have to be excluded by doing pulmonary function tests to exclude pulmonary causes. Also hepatic, renal and CNS tumors should be excluded by normal sonogram of abdomen, normal renal function and normal to low serum erythropoietin levels and normal CT/MRI of the posterior cranial fossa.

Treatment strategies include *phlebotomy, myelosuppressive* therapy, and general management. Phlebotomy is the initial treatment to control the manifestations of hyperviscosity and bring down the PCV to less than 45%. Myelosuppressive therapy is used to maintain the PCV at the desired level. ^{32}p is used for above 70 years. However, below, 60 years are given hydrea to effectively control the panmyelloisis and it is less leukemogenic. Alkylating agents, chlorambucil, is no more used for its high leukemogenic effects.

General management includes control of hypertension, with appropriate anti-hypertensive drugs; prutitis is helped by phlebotomies, antihistamines and H2 receptor blockers, it also help the peptic symptoms associated with the disease. Allupurinal effectively controls arthralgia and associated arthritis.

PV is an indolent disease attended by a waxing and waning course. Most of the morbidity and mortality is because of hemorrhage, thrombosis and vascular accidents. Median survival times, 10-16 years, are similar for phlebotomy, ^{32}p and chemotherapy groups of patients, with increased incidence of deaths from acute leukemia in those treated with alkylating agents (chlorambucil and busulfan).

Spontaneous transition to acute leukemia occurs in 2-5% and to Chronic Myeloid Leukemia (CML) and myelofibrosis in 30% of the cases. Hydroxyurea has currently been found to be the most effective and safe agent in the treatment of PV, especially in the young patients. Alpha interferon (IFN-Alpha), still in experimental stages, has been found to be effective in controlling the panmyellosis and has considerable future promise.

MATERIAL AND METHODS

This study was conducted at Hayat Teaching Hospital over years 1989 to 1996 and includes fifteen (15) selected cases of Polycythemia Rubra Vera (PV). There were thirteen male and only two female patients. The age ranged between 45 and 80 years.

Selection of patients was randomized according to the presenting clinical features, (Table–I) the relative incidence of various symptoms and signs. Detailed clinical history was followed by clinical examination to look for the specific signs. Final diagnosis was after laboratory work up (Table–II).

The tests done included Hb%, PCV, RBC count, TLC, DLC, ESR and platelet count. Arterial blood gases (P02) red cell mass estimations, serum uric acid was done in all so were X-Ray chest and ECG; other laboratory test done included ultrasound in all cases to exclude hepatic and renal neoplasm in particular and to confirm splenomegaly in general. CT scan brain was done in one case who presented with choreo-athetosis to exclude intracranial lesion, though chorea is a recognized feature of PV.

After final diagnosis was made the patients were treated accordingly. Treatment strategies included specific measures to bring down PCV to less than 45%, and included Phlebotomy, ^{32}p (for those $\geq$ 70 years), Hydrea (for those $\leq$ 60 years) and general treatment. Phlebotomy was done in all cases as the initial treatment. 200-500 mls of blood was removed at one sitting on alternate day until the PCV was brought down to 45-50%; Most of the patients responded with improved feeling of well being and fall in Hb%, PCV and red cell mass.

Maintenance phlebotomies were not possible as the patients resented too frequent bleeds. However, myelosuppression was used for maintenance purpose. Patients were stratified in two groups: Those treated with ^{32}p (the ^{32}p group) and those treated with hydrea the 'hydrea group'. In ^{32}p group one to two doses of ^{32}p were needed each of 3-2 mi Ci (2-5 m Ci/m2) at IRNUM Peshawar. The number of patients in this group was 10.

3 cases were given Hydrea at a starting dose of 1 gram then reduced to 500 mg until the PCV and the platelet counts were brought under reasonable control i.e, <45% and 4,000,00/cmm. The patient were asked to come after 2 weeks follow up and apart from detailed clinical examination to look for effect of treatment and find out any side effect of treatment repeat laboratory work up including Hb%, PCV, TLC, platelet count and uric acid estimations were also

TABLE – I

CLINICAL MANIFESTATIONS OF POLYCYTHEMIA VERA (PV)

Symptoms:	
CNS:	Dizziness (70%), Vertigo, Tinitis, Blurred vision, Diplopia, Involuntary movements (Chorea), Neurologic defects (Hemiplegia, Psychosis).
Gastrointestinal:	Epigastric pain (10-25%), Dyspepsia (40%) Upper gastrointestinal bleed, splenic pain (infarcts) Epistaxis, Renal Colic (uric acid stones)
Skin:	Pruritis 80%, Plethora (100%), Bruising, Burning sensations in feet and toes.
Cardiovascular:	Chest pain (angina), Intermittent Claudication, Venous and arterial thrombosis, and embolic events.
Musculoskelatal and Joints:	Painful swelling of joints (Gout), Arthralgia, and Feet pain.
Signs:	Plethora (100%), injected conjunctive, Dusky cyanosis Splenomegaly in 90% Hepatomegaly in one third cases. Hypertension (100%). Engorged Retinal veins (60%) Chorea (6%) Hemiplegias (strokes). Arthritis (secondary gout).

done and documented in the follow-up charts.

RESULTS

Total of 15 patients were included in this study, two were however lost to the follow up. The age ranged between 45 and 80 years; 68 years being the most incident age. Male vs female ration was 13 to 2. Common symptoms were pruritis (80%), dyspepsia (40%), epigastic pain (10-25%), dizziness and vertigo (70%). Common signs were general plethora (100%), splenomegaly (90%), dilated engorged retinal veins (60%), and hypertension in (100%). The results are tabulated in Tables: II a & II b.

The most sensitive tests were raised Hb%, red blood cell count, total leucocyte count and platelet count with a characteristically low ESR. The mean values for these markers in this study were: Hb% 19gm%, PCV 68%, TLC 14000/cmm, platelet count 65,000/cmm and uric 9gm%.

Specific tests included raised red cell mass averaging at 35 ml/kg for the 5 male patients in whom it was done (facilities for red cell mass estimation were not available later) and $P0_2$ estimation which averaged at 93%. Abdominal sonograms for hepatic, renal and other viscera were unremarkable; uterine sonograms in female patients were also reported normal. CT scan was done only in one case (presenting with chorea) and was reported normal; abdominal ultrasound also confirmed spleenomgally in those who did not have clinically detectable enlargement of spleen.

After final diagnosis the patients were treated initially with phlebotomy to bring down the hematocrit to reasonably safe levels to (<50). Maintenance therapy was then instituted with myelosuppressive agents

TABLE – II

DIAGNOSIS LABORATORY WORKUP

Test	Diagnostic reference Value	Mean for patient
HB%	18 gm%	19 gm%
PCV (hematocrit)	60%	68%
ESR (Very low)	03-mm ist hr	02 mm ist hr
Red Cell Mass	(26-34 ml/kg for male & 21 to 29 ml/kg for female)	35 ml/kg (on & for 5 pts)
TLC	10,000-20,000/cmm	14,000cm
Platelet count	More than 4, 50,000cmm	9 gm%
Panmyelosis	One bone marrow examination with absent iron stores	
Arterial PaO_2	≥ 92%	93%
High B_{12} levels		Not done
Normal or low erythropoietin level		yes
Normal renal and hepatic sonogram and CT/MRI		

either with ^{32}p or hydrea. Alkylating agents were not used in this study.

As a whole 12 cased were treated with ^{32}p, the ^{32}p group. Of these 10 cases had age ranging between 70-80 years, the remaining 2 each were of age 59 and 60 years respectively. But they could not afford hyrea and were also reluctant to go for frequent phlebotomies. So they wee also given ^{32}p at Irnum Peshawar.

The results of the treatment are summarized in Tables III, IV and V. The conclusions derived from this data are:

1. Phlebotomies are used as effective initial treatment strategy to alleviate the symptoms and prevent the complications; it can also be used as emergency procedure to bring down the PCV quickly before surgery. However, it cannot be used as a long term maintenance therapy, especially in our situation, where patients are too reluctant to opt for frequent phlebotomies.
2. ^{32}p is and effective myellosuppressive therapy for those ≥ 70 years, is less costly though its results are achieved relatively slowly.
3. Hydrea is an equally effective myelosuppressive therapy for those who are young (60 years) with more dramatic results but is costly and attended by side effects.

DISCUSSION

Polycythemia Rubra Vera (PV) is defined as increased red cell mass red cell count, packed cell volume (PCV), or hemoglobin level. In his early description of the disease William Osler realized that there are two main types of what he called as polyglobulism. True, in which there is a genuine increase in the

TABLE – III

PHELBOTOMY GROUP

	BEFORE TREATMENT	AFTER TREATMENT WITH PHLEBOTOMIES NUMBER OF PHELBOTOMIES				
MEAN	0	Ist	2nd	3rd	4th	5th
HB%	19	18.5	17	16.5	15	14.5
PCU	68	63	62	55	50	45
TLC	14000/cmm	16,000	15,000	12,000	12,000	12,000
Plat Count	600,000/cmm	650,000	650,000	700,000	700,000	700,000
Uric acid 5%	9 mg%	10mg%	8 mg%	8.5%	8 mg%	8 mg%

red cell mass, and the relative, in which there is a reduction in plasma volume with a normal red cell mass.[1,2] Same stands true today they are now called as absolute polycythemia and relative polycythemia. Absolute polycythemia is divided into primary polycythemia or poly-cythemia rubra Vera which is a myelo-proliferative disease of unknown aetiology and secondary polycythemia which results from a variety of different pathologic mechanisms (Table VI).[12] The causes of secondary polycythemia have to be excluded by specific tests in making a diagnosis of primary[5] polycythemia.

The cause of PV is unknown; there is no known risk to radiation exposure and no viral relationship for the disease has been found so far. The basic mechanism of PV is neoplastic change in the hemopoietic stem cell leading to excessive proliferation predominantly of erythroid but also of granulocytic and megakaryocytic precursors. Hence the result is panmyelosis i.e, increased red cell mass leucocytosis and thromboctyosis and this in one way differentiates PV from secondary polycythemia.[14] This increased proliferation of RBC precursors is independent of erythropoietin which is low or normal in

TABLE – IV

P GROUP

	BEFORE TREATMENT	AFTER TREATMENT				
DURATION YEARS	0	1	2	3	4	5
MEAN FOR						
Hb% gm%	17	16.5	15.5	15	15.6	14
PCV %	58	55	52	51	50	48
TLC/cmm	14000	13500	12500	12000	10000	9000
Plat: count/cmm	650000	500000	400000	300000	300000	300000
Uric acid mg%	8.5 mg%	7.9	8	7.4	7	6

TABLE – V

HYDREA GROUP

	BEFORE TREATMENT	AFTER TREATMENT				
DURATION	0	1	2	3	4	5
MEAN FOR						
Hb%	18.5	16.2	15	14.3	14.5	14
PCV %	62	52	47	49	47	45
TLC/cmm	15500	11000	9000	10000	10500	9000
Plat: count/cmm	650000	400000	300000	250000	300000	
Uric acid mg%	9	8	7.5	6.8	6.8	6.5

PV. The increase in red cell mass and PCV leads to increased viscosity of blood, increased blood volume and sluggish blood flow rates which alongwith the already atherosclerotic vessels of the above middle age and elderly patients of PV explains for most of the cerebrovascular and other peripheral vascular and organ manifestations of PV.[15]

Most of the clinical features and complications of the PV are the result of hypervicosity, hypervolemia, hypermetabolism and some platelet dysfunction. Hyperuricemia causes gout and increased basophilia manifests as pruritis. Presenting symptoms may involve almost any organ. Nonspecific complaints, probably related to circulating disturbances in the nervous

TABLE – VI

CLINICAL CLASSIFICATION OF POLYCYTHEMIA

Relative or Pseudo polycythemia:

True Polycythemia

A. Primary Polycythemia Rubra Vera (PV)

B. Secondary Polycythemia.

1. Altitude
2. Chronic lung diseases
3. Cyanotic congenital heart disease
4. Renal diseases: tumours, cysts, Hydronephrosis
5. Non renal tumors: hepatoma, cerebellar Hemangiomas, uterine Fibromata

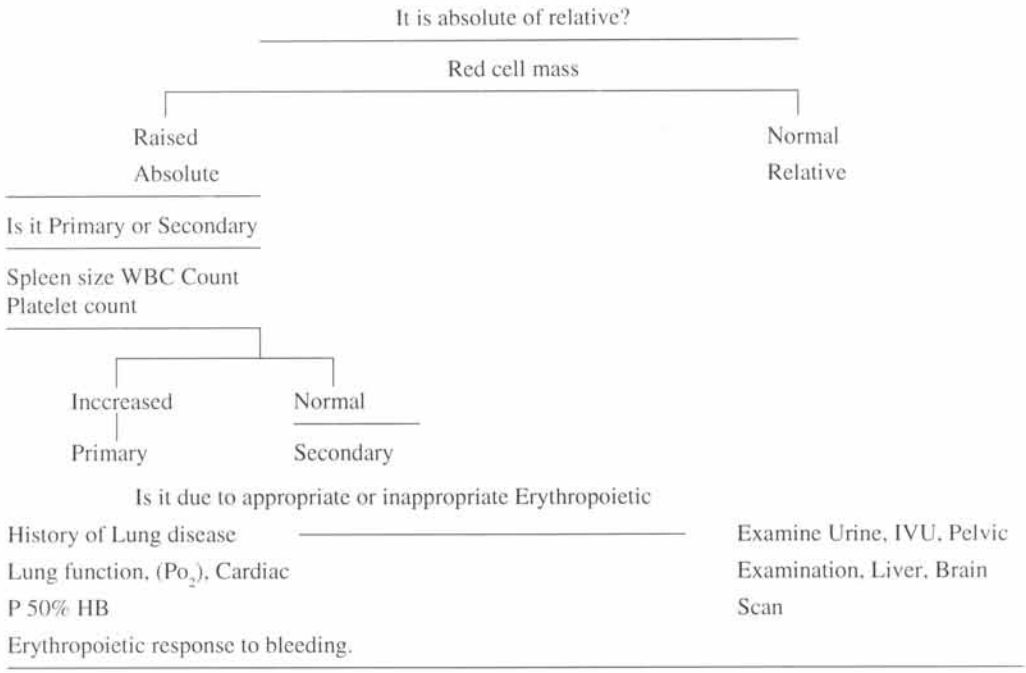
Endocrine: Cushings disease, pheochromocytoma.

Genetic: Abnormal hemoglobin, abnormal erythropoietic response, abnormal 2, 3 diphosphoglycerate metabolism.

Obesity: Pickwickian Syndrome, other causes of hypoventilation.

TABLE – VII

FLOW CHART OF INVESTIGATIONS FOR POLYCYTHEMIA



system, are the most common and include headache, dizziness, vertigo, tinitis, visual disturbances including blurring and diplopia. There may be a cardiovascular presentation with angina pectoris, intermittent claudication, or recurrent venous thrombosis or arterial embolic disease. Thrombosis may be either arterial of venous. Arterial thrombosis in turn may be cardiac, cerebral, or peripheral. Venous thrombosis may involve deep or superficial veins and cerebral, portal or hepatic veins.[5,6]

Other symptoms include an increased bruising tendency or more severe bleeding in the form of epistaxis, gastrointestinal hemorrhage, uterine bleeding (in female) or cerebral haemorrhage. Abdominal pain typical of peptic ulcer (5-10%) or left hypochondril pain due to splenomegaly may be another manifestation. A particular common symptom is severe and intractable pruritus worsened by warmth like hot both or getting into the bed at night. Burning feet and soles may be another miserable manifestation.

Physical examination typically shows plethora and there is a cyanotic tinge to the tongue, nose, ears and lips. The conjunctiva are injected and there is flush over the neck and the upper half of the truck. Splenomegaly is a feature in 75% of the cases, the size of the spleen varies greatly and ultrasound abdomen or C.T scan may be necessary to demonstrate that it is enlarged. A moderate hepatomegaly is present in one third of cases.[2,3]

Hypertension has been thought to be a common accompaniment, and tends to occur in one third of cases thought it may be because PV occurs at the age when hypertension is extremely common and it is doubted that this association is true.[6]

The diagnosis of PV is based mostly on clinical suspicion and confirmation by laboratory tests which are at first designed to confirm the polycythemia and second to differentiate it from secondary polycythemia. The flow chart (Table-VII) is reasonable guide to such a diagnostic approach. The various laboratory markers involved in diagnostic workup of PV are tabulated in Table-VIII and the workup for differential diagnosis in Table-IX. The treatment strategy is simplified as general management and specific measures. Specific measures are aimed at bringing down the PCV to less than 45% and maintaining the hematocrit (PCV) between 44 and 45%. Phlebotomy in indicated initially in all patients to reduce the hematocrit to less than 46%. In young patient with normal cardiac output a unit phlebotomy (500 mls) can be performed on alternate days until a safe hematocrit level is achieved. Patients with cardiovascular disease or elderly should have a smaller volume phlebotomies (200-300 mls) performed twice or once weekly. Phlebotomies, however, has its own limitations: patients are usually reluctant for opting for too many phlebotomies, patients managed by phlebotomy alone have a measurably high risk of thrombotic complications. Over a 5-7 years period after diagnosis iron deficiency anaemia is inevitable outcome with repeated phlebotomy.[3,7,10,11]

Myelosuppression is used to maintain the hematocrit at the desired level (below 45%) in those in whom it has been achieved with phlebotomies.[4,5] Myelosuppression is therefore required for the young who need frequent phlebotomies or whose disease is not controlled with phlebotomy or in those who have high platelet count and TLC despite frequent phlebotomies or the elderly with resistant disease. Alkylating agents like chlorambucil are no longer used as the results of Polycythemia Vera Study Group indicated more than 10% incidence of acute leukemia with their use.[9] ^{32}p (Radioactive phosphorus): this is an excellent therapy for older patients with severe disease. ^{32}p is a B-emitter with a half life of 14.3 days. It is concentrated in the bone and is the most effective mellosuppressive

TABLE – VIII

DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Category A:-

1. Significantly elevated red cell mass
2. Arterial blood Oxygen Saturation 92%
3. Splenomegaly

Category B:-

1. Thrombocytosis 400,000/Cmm.
2. Leucocytosis 12,000/Cmm.
3. Increased Leucocyte alkaline Phosphatase Score (Lap Score) in absence of fever or infection.
4. Serum B12 level greater than 900 Pg/ml or Vit B12 binding capacity greater than 2200 Pg/ml.

Diagnosis of Polycythemia Vera (PV) if:

1. AL + A2 + A3 Or
2. Al + A2 + any two factor from the category-B.

TABLE – IX

WORK UP FOR DIFFERENTIAL DIAGNOSIS

1. Serum erythropoietin (EP) concentration an elevated EP level suggests Secondary Polycythemia Normal or low EP level is compatible with PV.
2. Arterial blood Oxygen saturation PaO2 less than 92% suggests hypoxemia and favours diagnosis of secondary polycycthemia. Levels of PaO2 more than 92% are compatible with PV.
3. Direct carboxy hemoglobin and PaO2 levels are more helping in smokers as a cause of secondary polycythemia.
4. P50 of the Oxy-hemoglobin dissorciation curve is useful in detecting high oxygen affinity hemoglobin.
5. In PV neutrophie alkaline phosphatase levels are elevated.
6. Also is increase serum Vit B12 level and B12 binding capacity.
7. Radio graphic evaluation of kidneys, (to rule out erythropoietin secreting lesion) Liver (to exclude hepatomas) and posterior cranial fossa (to rule out cerebellar hemagiomata) may be necessary to exclude Secondary polycythemia in some cases.

agent. The usual remission time after a single dose is 2 years.[4] Following venesection to normal PCV, a dose of ^{32}p, 3 to 5 mi Ci (2.5 m Ci/m2) is given intravenously. Sometime a second smaller, 2-3 miCi of ^{32}p is required 2 month after the initial injection in order to bring the disease under complete control. The disease then remains quiescent for months or even years.[5]

For young patients (those 60 years or below) intermittent busulfan or hydroxyurea can be used. Hydroxyurea is a useful myelosuppressive agent. It should be started at a dose of 500 mg to 1 gm daily and the dose tapered down as control is achieved. Nausea, skin reactions and myelosuppression are the recognized side effects. Busulfan should be used at a dose of 4 to 5 mg daily until the platelet count is approaching normal; then the dose be reduced to 2mg daily until the normal platelet count is achieved. The drug should then be stopped and the patient carefully monitored.[10,11,16]

PV is an indolent disease attended by a waxing and wanning course. Most of the morbidity and mortality is because of haemorrhage, thrombosis and vascular accidents. Median survival times, 10-16 years, are similar for phlebotomy ^{32}p and chemotherapy groups of patients, though with increased incidence of deaths from acute leukemia in those treated with alkylating agents (chlorambucil and busulfan).[2]

Spontaneous transition to acute leukemia occurs in 2-5% and to CML and myelofibrosis in 30% of the cases. Hydroxyurea has currently been found to be the most effective and safe agent in the treatment of PV, especially in the young patients. Because it has been described to be less leukemogenic although it has to be proved in larger studies. Alpha interferon (IFN-Alpha) is still in experimental stages but has been found to be effective in controlling the panmyellosis and has considerable future promise.

CONCLUSION

Polycythemia Vera is not that uncommon as once thought. PV is mainly a clinical diagnosis confirmed by sensitive and specific laboratory tests. Our study differs with the literature review in two aspects: one that hypertension is a more common associationas against that reported in the literature review mentioning that it is

prevalent in only one third of the cases. And that control of hypertension is dramatically achieved with effective treatment of PV proving that this association is true rather than incidental.

Second ^{32}p is as effective as any other myelosuppressive therapy for those $\geq$ 70 years and is less costly, though it takes longer.

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