ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 08 | August - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CASE STUDY: JAK2 V617F NEGATIVE POLYCYTHAEMIA CAUSING PORTAL VENOUS HYPERTENSION WITHOUT EVIDENT PORTAL VEIN THROMBOSIS.

Hematology

Rajvi Chaudhary* Medical Student B.J. Medical college, Ahmedabad. *Corresponding Author

Neel Vora Medical Student B.J. Medical college, Ahmedabad.

Darsh Patel Post graduate second year resident, Department of medicine,B.J Medical college, Ahmedabad.

Kartikey G Parmar Professor and Head of Unit, Department of medicine,B.J Medical college, Ahmedabad.

ABSTRACT

Polycythaemia is defined as an increase in the haemoglobin above normal. This increase may be real or only apparent because of a decrease in plasma volume (spurious or relative polycythaemia). Often patients with polycythaemia are detected through an incidental finding of elevated haemoglobin or haematocrit level. Patients with polycythaemia may be asymptomatic or experience symptoms related to the increased red cell mass or the underlying disease process that leads to the increased red cell mass. The dominant symptoms from an increased red cell mass are related to hyper viscosity and thrombosis (both venous and arterial), because the blood viscosity increases logarithmically at haematocrits >55%. We are presenting a case of a patient aged 30 years presenting with fatigue, headaches, dizziness, recurrent multiple joint pain.

KEYWORDS

Polycythaemia, Budd–Chiari syndrome, JAK2 V617F mutation, Haematocrit, phlebotomy

INTRODUCTION

Polycythaemia is defined as an increase in the haemoglobin above normal. This increase may be real or only apparent because of a decrease in plasma volume (spurious or relative polycythaemia). The term erythrocytosis may be used interchangeably with polycythaemia, but some draw a distinction between them: erythrocytosis implies documentation of increased red cell mass, whereas polycythaemia refers to any increase in red cells. Often patients with polycythaemia are detected through an incidental finding of elevated haemoglobin or haematocrit levels. The dominant symptoms from an increased red cell mass are related to hyper viscosity and thrombosis (both venous and arterial), because the blood viscosity increases logarithmically at haematocrits >55%. Manifestations include neurologic symptoms such as vertigo, tinnitus, headache, and visual disturbances. Hypertension is often present. Patients with polycythaemia vera may have aquagenic pruritus, symptoms related to hepatosplenomegaly, easy bruising, epistaxis, or bleeding from the gastro intestinal tract. Peptic ulcer disease is common. Such patients also may present with digital ischemia, hepatic or splenic/mesenteric vein thrombosis, Budd–Chiari syndrome. Patients with hypoxemia may develop cyanosis on minimal exertion or have headache, impaired mental acuity, and fatigue.

For a normal healthy adult, the RBC mass is 23 to 29 mL/kg in females and 26 to 32 mL/kg in males.[1][2] Patients with haematocrit values greater than 51% and 48% and haemoglobin values greater than 185g/L and 165 g/L in males and females, respectively, usually have an elevated RBC mass.[3][4] Polycythaemia is not synonymous with erythrocytosis.

An elevated erythropoietin (EPO) level, usually as a secondary response to chronic hypoxemia, leads to secondary polycythaemia. Chronic hypoxemia can be secondary to various conditions, including lung pathologies like chronic obstructive pulmonary disease (COPD), airway pathologies like obstructive sleep apnoea as well as muscular abnormalities like obesity hypoventilation syndrome. [5]

We present a case of a 30-year-old man with no previously known medical conditions, who presented with chief findings of fatigue, headache, dizziness, recurrent multiple joint pain, skin patches with itching on the region around and patches are present on right hand, back and chest, whose CBC showed elevated haemoglobin and haematocrit, elevated erythropoietin and mutation analysis for JAK2 V617F was negative.

CASE STUDY

A 30-year-old male patient presented to our Orthopaedics department with chief complaint of multiple recurring joint pain since one and half years. The patient was receiving symptomatic treatment at an alternate hospital since the past few months with minimal improvement in symptoms. In addition, the patient also had complaints of headache, mild fever, abdominal pain, blurring of vision, diplopia, amaurosis fugax and slight loss of appetite, bruising, numbness in feet on prolonged use. Patient denied having chills, cough production, back pain, chest pain, pain on passing urine or stools, oral ulcers, dizziness, hearing loss, haemoptysis, haematochezia or epistaxis.

Past medical history is unrevealing. Patient sought medical advice in the previous year for similar complaints that are recurrent joint pains and headaches. But no conclusive diagnosis was found. History of TB, Hypertension, thyroid disorders, psychiatric diseases or any autoimmune diseases was otherwise not significant. His family history is significant for the death of his older brother from a similar hematologic condition. He denied use of tobacco, cigarettes, illicit drugs or alcohol consumption

On physical examination, he was oriented to time, place and person. His vitals showed pulse rate of 82 beats per minute, blood pressure was 130/80mmHg, the patients SPo2 was 96%. Evaluation of respiratory system was unremarkable with BLAE +, Cardiovascular system and GIT examination was normal as well.

Significant findings during imaging studies includes gall bladder calculi, for which the patient was referred to the surgical department and is now scheduled for an elective cholecystectomy.

Investigation

HIV ELISA test was non-reactive as was the serum testing for HbsAg and Anti HCV Ab. Serum testing for chikungunya and Dengue IgM antibody was also negative. Latest Hemogram revealed erythrocytosis with RBC count of 8.03* 10^6/ Cumm, Haematocrit 76% Haemoglobin level at 24.80 gm/dl ,RDWcv is 16.2%, WBC count 3.43*10^3/Cumm and Ab Lymphocyte count 617.00 cells /Cumm. Platelet count was also decreased at 88.00*10^3/Cumm. Erythropoietin levels were raised at 34.90 mIU/ml.Bone marrow Aspiration showed trilineage haematopoiesis without overt dysplastic features.
Metamyelocytes-BM 4.00% I (9.8 - 25.3 %),
Band Cells- BM2.00% L (8.5 - 20.8 %),
Polymorphs- BM 20.00% H (8 - 16 %),
Lymphocytes- BM 6.00% L (10.8 - 22.7 %),
Monocytes- BM 4.00% H (0.2 - 2.8 %),
Early Normoblasts-BM 7.00% H (0.7 - 3.7 %),
Inter Normoblasts- BM 10.00%L (12.2 - 24.2 %),
Late Normoblasts- BM 30.00 %H (2-22.7%)
Reticulocyte count was within the normal reference range at 0.6%.

Total bilirubin, direct bilirubin and indirect bilirubin levels were raised

at 5.72mg/dl, 0.52mg/dl and 5.20mg/dl respectively. Serum LDH was raised at 1591.00 IU/L. Serum electrolyte profile was normal except for Sodium and inorganic Phosphorus that were elevated at 156.45 mEq/L and 16.60 mg/dl respectively. Serum uric acid was also elevated at 8.40 mg/dl. Allele specific PCR testing for JAK2 V617F mutation was found to be NEGATIVE.

Imaging studies

Cect Scan Of Abdomen And Pelvis With Thorax revealed Portal vein appears dilated and measures approx. 17.5 mm at porta hepatis with dilated right & left main portal branches. Left branch of portal vein measures approx. 16.2 mm. Right branch of portal vein measures approx. 12.7 mm. Liver measures approx. 17.7 mm, suggest hepatomegaly. Spleen measures approx. 13.5 mm, suggest splenomegaly. Multiple collaterals are seen along porta hepatis, splenic hilum, tail of pancreas, lower oesophagus and gastro-oesophageal junction and leno renal area. Dilated venous channels / collaterals are also seen along lesser & greater curvature of stomach. Gall bladder appears partially distended and shows wall calcification along it, suggest Porcelain gall bladder.Intra-luminal hyper density is seen at neck of gall bladder, measuring approx. 6.5mm may suggest gall bladder calculus. Findings of thorax were normal.

Doppler study of bilateral lower limb arteries and veins for DVT was unrevealing. MRI study of the brain showed no acute infarct, intraparenchymal haemorrhage or SOL. Echocardiography revealed no structural abnormalities of the heart with LVEF at 55%

Treatment

Patient was ultimately DIAGNOSED with Secondary idiopathic Polycythaemia. During the hospital stay of roughly 1 month, patient was treated with daily Multivitamin Tablets and daily Aspirin. In addition, he was scheduled for phlebotomy twice (16 days apart) during the hospital stay, but showed minimal improvement in haematological status. Patient was ultimately discharged with advice of plenty of oral fluid intake. He was prescribed daily aspirin (75), Drotaverine hydrochloride tablet as an antispasmodic and phlebotomy once every 15 days, and is now showing significant improvement in clinical symptoms including joint pain, blurring of vision and headache.

DISCUSSION

The prevalence of polycythaemia vera has been estimated to be approximately 22 cases per 100,000 population. It is believed to occur more frequently among Jewish patients of Eastern European descent than other Europeans and Asians. Polycythaemia vera shows a male preponderance in all races and ethnicities, with a male to female ratio of approximately 2:1. The median age of presentation of PV is 60 years, with patients seldom seen before the age of 40. Polycythaemia due to hemoglobinopathies and congenital cyanotic heart diseases is likely to be detected in significantly younger patients. [1] In a study performed by Galeus et al. (2015), COPD, congenital heart disease, and severe pulmonary hypertension were found to be among the most common aetiologies of secondary polycythaemia. Data are lacking regarding the epidemiology of secondary polycythaemia. [2]

Secondary polycythaemia is due to an increased level of EPO or other transcription factors that, in turn, lead to an increase in the production of RBC mass. It should be noted that, unlike primary polycythaemia, there is no intrinsic defect in the erythroid progenitor cell lineage. [6] [7]

On the basis of the response of the erythroid progenitor cells to the circulating cytokines, polycythaemia can be further classified into primary or secondary.[3][4]

This endemic and recessively inherited congenital polycythaemia are named after the Chuvash people in central Russia. EPO levels have been found to be significantly higher than normal. [8]

A detailed history and thorough physical examination usually provide clues pointing towards secondary polycythaemia. A detailed history, including questions for each of the various etiological factors for secondary polycythaemia, can aid in the diagnosis. The patient should be asked about the smoking status, any history of weight loss, cough, palpitations, dyspnoea, snoring, as well as the family history that is pivotal in the diagnosis of congenital causes.[2] The patient should be asked about the usage of any anabolic steroids for muscle mass, as well as any prescription medication being used or recently used. Common presenting symptoms, usually non-specific, include fatigue, headache, dizziness, transient blurring of vision, amaurosis fugax, and other symptoms suggestive of transient ischemic attacks (TIAs). Infrequently, patients may complain of pruritus after a warm water shower, particularly over the back. A history of epistaxis, gastrointestinal (GI) bleeding, or easy bruising may be forthcoming.[1]

Peptic ulcer disease commonly coexists, and patients may present with non-specific abdominal pain. Left hypochondrial pain and early satiety should arouse the suspicion of splenomegaly. Rarely, patients may present with a history of unexplained thrombotic complications, such as Budd-Chiari syndrome or digital infarcts. [1]

On physical examination, scratch marks may be visible in these patients due to pruritus. Cyanosis and clubbing may also be seen. In patients who smoke, nicotinic staining of the nails and teeth can point to the underlying aetiology. The body mass index of the patient, as well as the alertness, can help in identifying obstructive sleep apnoea. A physical examination may reveal splenomegaly. Splenomegaly may, in turn, lead to early satiety as well. Hepatomegaly may be present in some patients. In cases with renal artery stenosis, a bruit may be heard on auscultation. [4] [9]

Renal diseases are also closely associated with secondary polycythaemia. In order to evaluate the presence of any renal aetiology, an intravenous pyelography, renal ultrasound, renal function tests, and computed tomography (CT) scan are required. In addition to that, liver ultrasonography, CT scan abdomen, and radionuclide scan are also warranted with possible hepatic aetiology. A CT scan of the brain with special attention to the posterior fossa can detect a cerebellar hemangioblastoma.[4][7] Gene mutations testing for EPOR, VHL, PHD2, and HIF2A can help to diagnose a congenital etiological factor.[7] World Health Organization Diagnostic Criteria for Polycythemia Vera are as follows - PV diagnosis requires meeting either both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria. Major criteria include – 1. Hb >18.5 g/dL (men)/>16.5 g/dL (women) or Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence or RBC mass >25% above mean normal predicted or Hb >17 g/dL (men)/>15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency, 2. Presence of JAK2 V617F or JAK2 exon 12 mutation. Minor criteria include – 1. BM trilineage myeloproliferation, 2. Subnormal serum Epo level, 3. EEC growth [10]

The discovery of the JAK2 V617F mutation, the definition of its frequency in PV and other myeloproliferative neoplasms, and the identification of its pathophysiologic implications, have transformed the diagnostic approach to PV from one based in the clinic and clinical laboratory to a truly molecular paradigm. JAK2 V617F has the potential to guide therapy of PV and other BCR/ABL-negative myeloproliferative neoplasms, whether as a therapeutic target or as a marker of response to therapy or of progression risk. A negative JAK2V617F can help differentiating between primary and secondary polycythaemia and thus ruling out polycythaemia vera.

The treatment approach in secondary polycythaemia depends on the aetiology involved. The general approach is the correction of the precipitating factors that will, in turn, lead to the correction of the hematologic abnormality.[4]

Patients who smoke should be advised to quit and be offered the appropriate supportive, psychological, and pharmacological intervention.

The management approach of secondary polycythaemia also varies with the development of complications. Low-dose aspirin may be useful in preventing thromboembolic episodes.[11] This is derived from the extrapolation of studies performed for polycythaemia vera. On a similar note, venesection has been found to be associated with a decreased risk of cardiovascular death and thrombosis in polycythaemia vera.[12] Extrapolation of these results for secondary polycythaemia is usually done, keeping in view the clinical judgment of the treating clinician.[7]

In these patients, phlebotomy is therapeutic with goals to maintain haematocrit values of 42% to 46%. Phlebotomy should be performed in any patient with secondary polycythaemia prior to any elective

surgery. In these patients, the therapeutic goal is the fine balance between adequate tissue oxygenation and hypervisocity.

CONCLUSION

Our case represents the rare finding of Jak2 negative polycythemia. The patient has evidence of portal vein hypertension, although there was no conclusive evidence indicating portal venous thrombosis. It is crucial to carry out thorough genetic testing as the disorder could be prevelant in other family members as well.The most commonly prescribed treatment modality in such cases is a routine phlebotomy.

REFERENCES

1. Polycythemia - StatPearls - NCBI Bookshelf (nih.gov)
2. Secondary Polycythemia - StatPearls - NCBI Bookshelf (nih.gov)
3. Maran J, Prchal J. Polycythaemia and oxygen sensing. Pathol Biol (Paris). 2004 Jun;52(5):280-4. [PubMed]
4. Hocking WG, Golde DW. Polycythaemia: evaluation and management. Blood Rev. 1989 Mar;3(1):59-65. [PubMed]
5. Nadeem O, Gui J, Ornstein DL. Prevalence of venous thromboembolism in patients with secondary polycythemia. Clin Appl Thromb Hemost. 2013 Jul-Aug;19(4):363-6. [PMC free article] [PubMed]
6. Percy MJ, Furlow PW, Beer PA, Lappin TR, McMullin MF, Lee FS. A novel erythrocytosis-associated PHD2 mutation suggests the location of a HIF binding groove. Blood. 2007 Sep 15;110(6):2193-6. [PMC free article] [PubMed]
7. McMullin MF. Investigation and Management of Erythrocytosis. Curr Hematol Malig Rep. 2016 Oct;11(5):342-7. [PubMed]
8. Prchal JT. Molecular biology of polycythemias. Intern Med. 2001 Aug;40(8):681-7. [PubMed]
9. Pillai AA, Fazal S, Babiker HM. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Nov 3, 2021. Polycythemia. [PubMed]
10. Diagnosis and Management of Polycythemia Vera - PMC (nih.gov)
11. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, Barbui T., European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004 Jan 08;350(2):114-24. [PubMed]
12. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, De Stefano V, Elli E, Iurlo A, Latagliata R, Lunghi F, Lunghi M, Marfisi RM, Musto P, Masciulli A, Musolino C, Cascavilla N, Quarta G, Randi ML, Rapezzi D, Ruggeri M, Rumi E, Scortechini AR, Santini S, Scarano M, Siragusa S, Spadea A, Tieghi A, Angelucci E, Visani G, Vannucchi AM, Barbui T., CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythaemia vera. N Engl J Med. 2013 Jan 03;368(1):22-33. [PubMed]