VOLUME-7, ISSUE-11, NOVEMBER-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Medicine

A RARE CASE OF RECURRENT CEREBROVASCULAR STROKE DIAGNOSED AS HAVING POLYCYTHEMIA VERA (JAK-2 MUTATION)

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ABSTRACT Cerebrovascular stroke is a very commonly encountered medical emergency. Physicians need to be thoroughly trained in stroke work up and its management. Hereby, we aim to discuss polycythemia vera, JAK-2 mutation as one of the miscellaneous causes of recurrent Cerebrovascular stroke and its management.

KEYWORDS : recurrent CV stroke, polycythemia Vera, JAK-2 mutation

I. INTRODUCTION

JAK-2 is a member of non receptor tyrosine kinase Family, that functions as an obligate chaperone for erythropoietin & thrombopoietin receptor in the golgi apparatus and is responsible for cell surface expression. Binding of erythropoietin & thrombopoietin to its respective receptors leads to autophosphoryation of JAK-2 & other Proteins involved in cell proliferation, differentiation and its resistance to apoptosis. Constitutive activation JAK-2 leads erythropoietin independent erythroid colony formation and their resistance to apoptosis. Eventually, there is hypersensitivity of erythroid progenitor cells to erythropoietin & other hematopoietic growth factors, increased rate of terminal differentiation and increase in expression of Bcl-xl - all accounting to polycythemia vera.

Polycythemia vera is a clonal disorder of multipotent hematopoetic progenitor cell in which phenotypically normal red cells, granulocytes and platelets accumulate in absence of recognizable physiologic stimulus. Polycythemia vera is the most common of all chronic myelopreliferative disorders with incidence of 2/100000. Incidence increases with age to as high as 18/100000 lac. About 30% cases of Polycythemia Vera are attributed to chromosomal abnormalities 20q and trisomy 8 and 9 whilst most of the cases are attributed to mutation of autoinhibitory pseudokinase domain of tyrosine kinase JAK-2 that replaces valine with phenylalanine (V617F) causing constitutive activation of the kinase.

JAK-2 gene is located on the short arm of chromosome 9 & loss of heterozygosity on chromosome 9p due to mitotic recombination is the most common of all cytogenetic abnormalities in polycythemia vera. Loss of heterozygosity in the JAK-2 locus of 9p leads to homozygosity for mutant JAK-2 V617F. Predisposition to acquire mutations in JAK-2 appears to the associated with specific JAK-2 haplotype GGCC. More than 90% patients of polycythemia vera express JAK-2 mutation whilst its observed in only 50% cases of progressive myelofibrosis and essential thrombocytosis. Homozygosity is observed in 30% cases of polycythemia vera & 60% cases of progressive myelofibrosis. Some of the heterozygotes turn homozygotes for JAK-2 mutation over 10 years of the natural course of the disease.

Clinical features of polycythemia vera

In most of the cases, polycythemia vera is an incidental discovery of high Hb or hematocrit. Symptoms of polycythemia vera are accounted to uncontrolled erythrocytosis, vascular stasis, thrombocytosis and large turnover of hematopoietic cells with increased cytokine activation.

Symptoms d/t erythrocytosis induced hyperviscosity

May include → neurological symptoms - vertigo, tinnitus, headache & visual disturbance (ocular migrane)

Erythromelalgia- erythema, burning & pain in the extremities

Arterial & venous thrombosis- Ischemic stroke or venous hemorrhagic infarcts, acute coronary syndrome or hepatic vein thrombosis leading to budd chiari syndrome

Consequences of vascular stasis & thrombocytosis in git may include git hemorrhage, peptic ulcer disease and splenomegaly (which may be the only initial presenting sign of polycythemia vera) Whereas large turnover of hematopoietic cells leads to secondary hyperuricemia and gout, increased cytokine & basophil activation by JAK-2 V617F accounts to constitutional symptoms & aquagenic pruritus.

II. CASE REPORT

Mr. Ganpatbhai Shakrabhai Patni, 70 year old, Male, chronic smoker was admitted in the emergency room of civil hospital Ahmedabad on 22/09/18 with chief complains of one episode of generalized tonic clonic convulsion 2 days ago followed by sudden onset altered sensorium. Patient had no h/o fall,trauma,fever. Patient was a k/c/o CHRONIC OBSTRUCTIVE PULMONARY DISEASE,DIABETES MELLITUS TYPE 2, HYPERTENSION & CV stroke as MRI Brain (dated 31/10/17) was suggestive of focal area of gliosis in right Cerebellum,right frontal periventricular white matter. Patient was on regular R_x T amlo (5mg) OD, T atenolol (50mg) OD, T aspirin(150mg) OD, T Atorvas (40 mg) HS, T acebrophylline (100mg) TDS.

EXAMINATION

On examination patient was unconscious, response to deep pain stimuli was present.

The other finding were as follows

Temperature -normal
Pulse- 82/min
Blood Pressure-150/90 mm Hg
Tongue , conjunctiva ,nail – pink
Sclera - white
Respiratory system – Normal
Cardiovascular system – Normal
Abdominal Examination – Soft, mild splenomegaly present
No obvious enlargement- of thyroid and other lymph nodes noted.

CNS- Unconscious, Response to DPS – present, moving right u/l & l/l
Pupils - B/L normally reacting to light

Plantar – Right side upward Left Side Downward
Tone – ↓ in all 4 limbs. No Neck rigidity
Reflexes- B ++
T + +
S ++
K++
A++

INVESTIGATION

NCCT Brain (24/09/18)

Acute lacunar infarcts in right gangliocapsular ,left thalamus, right parietal periventricular region , B/L perisylvian region and gliosis in right parietotemporal region+right inferior cerebellum + porencephalic cyst in right parietal periventricular region

CXR - NAD
ECG- NSRWNL
Fundus – WNL

2D Echo – LVEF 55%. No RWMA at chest, No valvular abnormality noted

USG(A+P)- liver normal in size & mildly altered in echotexture, few GB Calculi, spleen (15.5cm) & few hyperechoic lesions (Calcified lesions) p/o old granulomatous lesion

LABORATORY INVESTIGATION

Hb	-20.10 g/dl
WBC	-27900/cumm
RBC	-8.56 × 10^6/cu mm
Hematocrit	-69%
Platelets	-2.24 L
MCV-	88fl
RDW	- 15.10
DC	81/13
Lymphocyte	– 13%
Eosinophils-	3%
Monocytes	3%
Basophils	0%
MCH	32pg
MCHC	36g/dl

P/S	– normocytic normochromic
RBC	-mass increased Leucocytosis with neutrophilia
MP	- NS
TB	-1.11 mg/dl
DB	-0.20 mg/dl
SGPT	-11 U/L
SGOT	-38U /L
ALP	-105 U/L
TP	-7.06 g/dl
ALB	-4.43 g/dl
UREA	-29.70 mg/dl
CREAT	-1.09 mg/dl
Na^+	- 138 mEq/L
K^+	-4.2 mEq/L
RBS	-143
HIV	-NR
HBsAg	-NR
ESR	- 8
Ferritin	-345.30 ng/ml
Ca	-8.38mg/dl
Po4	-2.86mg/dl
UA	-9.44 mg/dl

Lipid Profile

Cholesterol	- 152.77 mg/dL
TG	-125 mg/dl
HDL	- 36.20mg/dl
VLDC	-25
LDL	-91.57 mg/dL
CHOL/HDL	-4.21
CHOL/VLDL	-6.11
CHOL/LDL	-1.61

Erythropoetin	- 70.1
JAK-2 (V617F)	Mutation- Positive

COURSE IN HOSPITAL

Patient was admitted in hospital on 22/9/18 in unconscious state. Routine investigations done were s/o polycythemia. NCCT brain done s/o multiple acute lacunar infarcts and multiple areas of gliosis

Patient was empirically treated with antiplatlet, statins, anticonvulsant valproate and mannitol. A thorough work up for stroke was done. Erythropoetin was mildly elevated while JAK-2 mutation was positive. Diagnosis of polycythemia vera was established and patient was made to undergo three cycles of phlebotomy (300ml blood removed in each cycle) over a period of 5 days to achieve a target hematocrit of <45% . Patient lost consciousness due to raised intracranial tension , went into sudden cardiorespiratory arrest and died on 2/10/18.

III. DISCUSSION REGARDING TREATMENT OF POLYCYTHEMIA VERA

To avoid thrombotic complications, a maintenance Hb level <14g/dl & hematocrit of <45% in men & in women Hb level of <12g/dl & hematocrit of 42% is mandatory.

Initially phelobotomy serves to reduce hyperviscosity by bringing red cell mass to normal range. Thereafter, periodic phlebotomy serves as maintenance by inducing a state of Iron deficiency & thus preventing accelerated re-expansion of red cell mass.

Once an iron deficient state is achieved periodic phlebotomy is required every 3 month. Use of aspirin is not of proven role if increased red cell mass is not controlled by phlebotomy.

If hyperuricemia (< 10 mg %) is asymptomatic, it does not require any treatment, but if chemotherapy is employed to treat leucocytosis or splenomegaly or if there is intractable pruritus- allopurinol should be administered.

Symptomatic splenomegaly is to be treated with pegylated interferon α.

Anagrelide, a phosphodiesterase inhibitor is preferred over hydroxyurea to reduce the platelet count in case of erythromelalgia or ocular migrane as it lacks bone marrow toxicity and is protective against venous thrombosis.

Hydroxyurea, alkylating agents and radioactive P^{32} being leukemogenic, shoud be avoided.

Other modalities of treatment include splenectomy in patients with intractable weight loss, allogenic bone marrow transplant in young patient and JAK-2 inhibitors under trial like fedratinib and ruxolitinib.

IV. KEY MESSAGE

In young patient with no obvious risk factors for stroke or before labeling as cryptogenic stroke, a possibility of polycythemia should be kept in mind according to blood counts. Or even in patients with obvious with risk factors for stroke, a careful watch over blood counts may help in early diagnosis of myeloproliferative neoplasms and thus improving the prognosis and survival chances of the patients.

REFERENCES

1. Harrison's principle of internal medicine 19th Edition chapter polycythemia vera
2. www.ncbi.nlm.nih.gov>pubmed
3. www.bloodjournal.org>2017/05/12
4. www.strokejournal.org>abstract