

Polycythemia Vera Complicated by Portal Vein Thrombosis and Budd-Chiari Syndrome:

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ABSTRACT:

Polycythemia vera is a medical condition characterized by raised hematocrit. Owing to increased viscosity, the blood flow in the vessels become sluggish leading to the clinical features of polycythemia such as headache, blurring of vision, red skin, dizziness, raised blood pressure, itching and more serious medical events like vaso occlusion, thrombosis and strokes. In this case report, polycythemia vera presenting unusually with heamatemesis, melena and abdominal distension. Physical examination of this case revealed massive ascites with dilated veins around the umbilicus. The diagnosis of polycythemia vera complicated by Budd Chiari Syndrome and Portal Vein Thrombosis was made. Patients with polycythemia vera are at risk of vaso occlusive sequelea like portal vein thrombosis and Budd chiari syndrome.

Key words: Budd chiari syndrome, Polycythemia Vera, Portal vein thrombosis.

INTRODUCTION:

Polycythemia vera is a disorder which is characterized by excessive production of red blood cells by the bone marrow. It may also lead to over production of white blood cells and platelets.¹ The WHO criteria for the diagnosis of polycythemia vera is as follows:

Major Criteria:

- 1) Heamoglobin >18.5 g/dl in men, Heamoglobin >16.5 g/dl in women
- 2) JAK 2 MUTATION or other functionally similar mutations

Minor Criteria:

1. Bone marrow biopsy revealing trilineage growth , hyper proliferation of erthrocytic, granulocytic and megakaryocytic precursors.
2. Serum erythropoietin levels below the lower limit of normal range.
3. Endogenous erythroid colony formation in vitro.

Diagnosis of polycythemia vera requires two major criteria plus one minor criterion OR 1st major criterion plus two minor.²

Patients with polycythemia vera are at on higher risk of thrombus formation and vaso occlusive crises attributable to the blood being thicker and sluggish to flow. The clinical

course of the disease is characterized not only by thrombotic complications but also by transformation to leukemias and myelofibrosis, thus causing increased mortality and morbidity. Increasing age, previous history of thrombotic events and marked leukocytosis are the major risk factors for thrombotic complications in polycythemia vera. Portal vein thrombosis (PVT) and Budd-Chiari syndrome both are splanchnic vein thrombosis. Despite of features suggesting PVT ,the cell counts are not markedly raised due to iron deficiency, spleenomegaly and heamodilution thus rarely fulfilling the diagnostic criteria of polycythemia vera with these complications. BCS is characterized by hepatic vein outflow obstruction. It can be primary when the source is endo luminal i.e. pro thrombotic states and its secondary when the cause is extra vascular i.e. any tumor compressing from outside or any invasion. The etiology of primary BCS includes pro thrombotic disorders like myeloproliferative neoplasms, anti-phospholipid antibody syndrome, protein C, protein S deficiency, factor V Laiden mutation.³ Polycythemia vera is the most frequent cause of BCS and is seen in around 40% of the diagnosed cases.⁴ Portal vein thrombosis in the absence of liver cirrhosis and local malignancy is less frequently encountered and shows an etiological overlap with primary BCS. Acute portal vein thrombosis with associated portal hypertension presenting with massive heamatemesis could be the initial presentation of polycythemia vera in previously asymptomatic patient. The strong relationship between Myeloproliferative neoplasms and splanchnic vein thrombosis would help the clinicians to screen the patients with MPN for SVT and vice versa. Hence the purpose of reporting this case was to highlight the clinical and molecular basis of MPN associated splanchnic vein thrombosis.⁵

CASE REPORT:

A 50 years old man presented to medical ward of Sandeman Provincial Hospital Quetta on 13th February 2020 with abdominal distension since two months, heamatemesis and melena since 3 days. Abdominal distension was gradual and

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was associated with dull aching pain. He was afebrile and had no history of dark urine, head ache, seizures, loss of consciousness or itching. The family history revealed chronic myeloid leukemia in one of his brothers and was taking treatment for it. On examination the patient had congested lower conjunctiva without plethora. There was no evidence of jaundice. Patient had massive ascites with caput medusae and was mildly edematous.

Initial labs of the patient revealed the following; Hb 13.3g/dl, HCT 36.4%, MCV 70.2 fL, WBCs 19350/cmm, platelets 870000/cmm, ESR 09 mm/hr. Serum erythropoietin level was 3.75 IU/L i.e. around the lower limit of normal range. The liver function tests revealed ALT of 161 U/L, normal albumin and prolonged PT of 28 sec. His renal function tests and serum electrolytes were within the normal range. Viral marker were negative and an ultrasound of the abdomen showed massive ascites with cirrhotic liver, mild splenomegaly, dilated portal vein measured 1.8 cm, there was a thrombus in the portal vein. Moreover a Doppler ultrasound was performed which revealed absence of blood flow in the hepatic veins with partial thrombi in the inferior vena cava in addition to above mentioned USG findings. The ascitic fluid cyto chemical analysis showed a transudative picture with high SAAG ratio suggestive of portal hypertension. Upper GI endoscopy was performed which revealed grade III esophageal varices for which band ligation was done and the patients was started beta blockers too. Bone marrow biopsy was done and showed erthroid hyperplasia, hyper proliferation of granulocytes precursors and megakaryocytes precursors. JAK 2 mutation test was ordered which came out to be positive and highly suggestive of myeloproliferative neoplasm with negative bcr-abl by FISH . A diagnosis of polycythemia vera complicated by Budd-chiari syndrome and portal vein thrombosis was finally made.

The patient was treated on the line of chronic liver disease. Later on when he became stabilized clinically, he was kept on low molecular weight heparin followed by oral anti-coagulants. His phlebotomy sessions were done in order to keep his hematocrit with the normal range. Low dose aspirin was added to the treatment in order to prevent pro thrombotic complications after routine phlebotomy and routine anti-coagulant therapy. JAK 2 inhibitor therapy Ruxolitinib was started for the underlying MPN i.e. polycythemia vera.

DISCUSSION:

The patient's normal Hb and HCT with low MCV could be attributed to hematemesis due to underlying portal hypertension induced variceal bleeding. Polycythemia is a stem cell disorder characterized by pan hyperplastic, malignant and neoplastic bone marrow. It's most prominent feature is increased red cell mass due to uncontrolled red blood cells production along with increased white blood cells and platelets production due to abnormal hematopoietic

stem cells⁶. The JAK2 V617F mutation being present in 90-95% of polycythemia vera patients and in around 50% of ET essential thrombocytosis and myelofibrosis patients is used as a non-invasive diagnostic tool⁷. The mutation enhances the proliferative capacity of all erythropoietin independent erythroid colonies. Polycythemia vera is thus characterized by panmyelosis with significant quantitative and qualitative defects affecting all three cells lineages.

MPNs with negative Philadelphia are the most frequent pro thrombotic factor in splanchnic vein thrombosis. Hyper viscosity rendered by increased red cell mass in polycythemia vera is not the only factor leading vaso occlusive events, JAK 2 mutations also causes hyper sensitivity to cytokines which leads to production of pro thrombotic factors and adhesion molecules in the vessel walls.⁷ The strong association between MPNs and portal vein thrombosis and Budd-Chiari syndrome was confirmed by the high frequency of JAK2V617F amongst these patients , present in 17-35% and 30-45% respectively. JAK2 Mutation not only defines the molecular basis of the disease but also responsible for its raised hematocrit, thrombotic events, pruritus and response to hydroxyurea^{8,9}. JAK2 mutations have frequently seen in patients with splanchnic vein thrombosis thus JAK2 mutation screening has become a part of diagnostic work up in SVT⁸. Anti-coagulants along with diuretics are the main stay in the treatment of BCS in the absence of hepatic insult. However balloon angioplasty with stent placement also have roles. Interventions are done in patients with inferior vena cava involvement. The current recommendation for the treatment of acute portal vein thrombosis is anti-coagulation for at least 3 months aiming a target INR 2.0-3.0¹⁰. For polycythemia vera phlebotomy being the mainstay in the management, low dose aspirin is recommended to prevent the thrombotic complications like acute myocardial infarction, stroke and major thromboembolic events. However myelosuppressive therapy, hydroxyurea and JAK2 inhibitor Ruxolitinib are also used.^{10, 11}

CONCLUSION:

The risk factors for occurrence of SVT in MPN includes JAK2V 617F mutation, young age, female gender and concomitant other hypercoaguable states. Our case highlights a clear cut relationship between myeloproliferative neoplasms and incidence of splanchnic vein thrombosis. Understanding this association has significant implications on disease management and prognosis. The treatment of MPN should be started immediately as any delay could end up taking patient's life. Hence identifying the patients at risk of SVT and managing accordingly can considerably decrease the mortality and morbidity.

REFERENCES:

1. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. *Blood*. 2014;124:3685–3691.

2. Noronha Ferreira C, et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. *Hepatology*. 2016;63:1640–1650.
3. De Stefano V, Qi X, Betti S, Rossi E. Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment. *Thromb. Haemost.* 2016;115:240–249v
4. Lavu S, et al. Splanchnic vein thrombosis in patients with myeloproliferative neoplasms: the Mayo clinic experience with 84 consecutive cases. *Am. J. Hematol.* 2018;93:E61–E64
5. Gianelli U, et al. Discrepancies between bone marrow histopathology and clinical phenotype in BCR-ABL1-negative myeloproliferative neoplasms associated with splanchnic vein thrombosis. *Leuk. Res.* 2015;39:525–529.
6. Finazzi G, Ageno W. Direct oral anticoagulants in rare venous thrombosis. *Intern. Emerg. Med.* 2016;11:167–170
7. Raskob GE, et al. Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N. Engl. J. Med.* 2018;378:615–624
8. De Gottardi A, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int.* 2017;37:694–699.
9. Barbui T, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018;32:1057–1069.
10. Harrison CN, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. *Blood*. 2017;130:1889–1897
11. Mead AJ, et al. Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial. *Br. J. Haematol.* 2015;170:29–39.

