

# Portal Vein Thrombosis in a Case of Chronic Myeloid Leukemia- a Rare Association

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## Abstract

Chronic Myeloid Leukemia (CML) in absence of hyperleukocytosis is an unusual cause for hepatic vein thrombosis. We present a case of hepatic vein thrombosis that presented with abdominal pain, vomiting and splenomegaly. Ultrasound and Doppler study findings indicated hepatic vein thrombosis. His thrombophilia profile was normal. However he had slightly raised platelet count and mild leukocytosis at that time. He showed improvement on anticoagulant therapy. However after two years he presented with weakness and was suggested bone marrow biopsy and cytogenetic studies. The findings of these tests were in favour of CML in chronic phase and cytogenetic studies revealed Philadelphia positivity. He was not evaluated for thrombocytopenia though he had raised platelet count at the time of presentation. He is now receiving treatment for CML. It is proposed that the patient may have developed essential thrombocythemia in addition to Philadelphia positive CML, thereby making the patient prone to thrombotic episodes even at an early stage of CML. Unfortunately he could not be evaluated for JAK-2 mutation at any stage. It is suggested that in absence of hyperleukocytosis patients with history of thrombosis should be evaluated for myeloproliferative disorders (MPDs) as treatment for these disorders itself reduces the size of thrombus.

**Key words:** Hepatic vein thrombosis, MPDs, CML, Essential thrombocythemia, Thrombocytosis, Hyperleukocytosis

## Introduction

Portal vein thrombosis (PVT) is one of the rare causes of splenomegaly and can present with acute, sub-acute or chronic onset. It usually presents with pain in abdomen, which may be colicky or vague with or without haemetemesis/malena. PVT has many causes including prothrombotic genetic defects such as protein-C, protein-S and antithrombin-III deficiency, hypercoagulation states such as latent myeloproliferative disorders, antiphospholipid syndromes, hematologic disorders like paroxysmal

nocturnal hemoglobinuria and sickle cell diseases, pregnancy and use of oral contraceptives, etc. Among these, myeloproliferative disorders (MPDs) are a known cause for bleeding as well as thrombosis. Thrombosis occurs in approximately one third of cases of MPDs, particularly PV and ET, contributing to a mortality of 15% to 40%.<sup>1,2</sup> It may involve arteries or veins, more frequently affecting arteries. In some cases the condition involves unusual sites such as portal or retinal veins. The cardiovascular system is involved in rare cases and acute ischemic coronary artery disease is the presenting symptom in some cases.

Both hemorrhagic and thrombotic episodes account for the morbidity and mortality in myeloproliferative diseases (MPD). These may be related to acquired platelet abnormalities observed in some patients such as increased platelet production, altered platelet secretory granular content, changes in glycoprotein concentrations and abnormal response to aggregating agents especially epinephrine. Among MPDs, thrombosis is comparatively more commonly seen in Thrombocytopenia and Polycythemia Vera and is rarely seen in CML. The pathogenetic contribution of granulocytes to thrombosis in MPDs might involve 'cross-talk' between granulocytes and platelets and/or endothelial cells. Compared with healthy controls, patients with ET or PV display increased baseline/induced platelet P-selectin expression, platelet-granulocyte/platelet-monocyte complexes, granulocyte activation (increased CD11b expression, etc), and baseline/lipopolysaccharide-induced expression of tissue factor (TF) by both monocytes and neutrophils. Furthermore, these abnormalities might be more pronounced in patients with history of thrombosis and in those with JAK2V617F.<sup>3</sup> Changes in viscosity state due to hyperleukocytosis and thrombocytosis is a cause of thrombosis in CML. However the risk of thrombosis in CML is very low as compared to PV and ET, although thrombocytosis is commonly seen with it.<sup>4</sup>

We present a case of 32 years old male who presented with abdominal pain and on ultrasound was diagnosed as a case of hepatic vein thrombosis. He was put on anticoagulant therapy and after about two and half years was diagnosed as a case of Philadelphia positive CML

### **Case Report**

A 32 years old male presented with unrelenting abdominal pain, diarrhoea and vomiting in 2011. His physical examination was unremarkable except for mild splenomegaly and he was advised ultrasound abdomen. The findings on ultrasound were portal vein thrombosis and splenomegaly. Doppler ultrasound abdomen also showed portal vein thrombosis. On Blood complete picture performed at that time, the white cell count was  $15.6 \times 10^9/l$ , Hb level was 11.9 g/dl and platelet count was  $482 \times 10^9/l$ . Findings of Peripheral blood smear included normocytic normochromic anemia with 69% neutrophils, 13 % lymphocytes, 2% monocytes, 3% Eosinophils, 10% Basophils, 2% myelocytes and 1% metamyelocytes. LFT done showed bilirubin 0.6% (Reference: 0.2-1.1mg/dl), ALT: 49 IU/L (Reference: 9-40), AST: 40IU/L (Reference: 9-40) and Alkaline phosphatase 115 IU/L (Reference: 30-115). Thrombophilia profile was normal and he was put on anticoagulant therapy for portal vein thrombosis. Initially he was receiving Injection Klexin 1 x OD for one year and then he was put on warfarin with monitoring of INR. Meanwhile his CP was done; it showed white cell count of  $11.6 \times 10^9/l$ , Hb 11.8 g/dl and platelet count:  $618 \times 10^9/l$  with neutrophils 60%, lymphocytes 30%, Monocytes 6%, Eosinophils 4%, myelocytes 2% and metamyelocytes 1%. He was on the same treatment till in March 2013 when he started complaining of weakness, vertigo and dyspnea on exertion. This time his CP showed TLC of  $28.4 \times 10^9/l$  with Hb of 14.5g/dl and platelet count of  $626 \times 10^9/l$ . Peripheral smear examination showed neutrophilic leukocytosis with left shift and prominent basophils. Bone marrow biopsy findings were suggestive of CML in chronic phase. Trepine biopsy showed hypercellular bone marrow fragments with hyperplastic myeloid series cells and increased megakaryocytes. Fibrosis was prominent in some areas. Cytogenetic studies on blood and bone marrow showed presence of Philadelphia Chromosome and treatment for CML was initiated. He could not be tested for JAK 2 mutation at any stage.

### **Discussion**

Myeloproliferative disorders (MPDs), whether overt or latent, represent a main risk factor for the development of thrombosis in the portal, mesenteric, and hepatic areas.<sup>5-7</sup> Venous thromboses significantly affect morbidity and mortality of patients with MPD and are associated with severe organ damage and high mortality.<sup>8</sup> It is well-known that portal and mesenteric venous thrombosis (PMVT) may be an early or presenting complication of an undiagnosed MPD, particularly in young patients and that a proportion of these patients do not even fulfil the diagnostic criteria for MPD but have features suggestive of a latent form based on hyperplastic bone marrow and erythroid progenitor cell culture; these cases may subsequently develop overt MPD as is the case with our patient. In a previous study, a meta-analysis of 120 patients from seven studies indicated that the estimated incidence of underlying MPD depends on the diagnostic criteria used.<sup>9</sup> Although leukemic thrombi are a well-known complication of acute or chronic myeloid leukemia, they tend to occur most commonly in the setting of hyperleukocytosis when the leukemic cell burden is remarkably high ( $\geq 100 \times 10^9/l$ ).<sup>10,11</sup> Changes in blood flow occur secondary to elevated leukocyte counts, which may affect blood flow, particularly when leukocytosis is extreme (more than  $300 \times 10^9/l$ ). Condition of the patients improves when put on treatment which leads to fall in total WBC count. However, rarely patients do present with thrombotic complications in the absence of hyperleukocytosis or even elevated leukocyte counts.<sup>12</sup>

Janus kinase 2 (JAK2) V617F mutation, an acquired mutation that occurs in MPD patients, is also risk factor for PMVT independently of the presence of overt MPDs. In one of the studies done by Colaizzo et al over a 10-year period of observation of the 99 patients presenting with PMVT, the JAK2V617F mutation was detected in heterozygous state in 17 (17.2%) individuals. None of the patients presenting with the JAK2 V617F mutation carried an inherited thrombophilic risk factor.<sup>13</sup> In another study conducted by Abedeen et al, JAK2 mutation was detected in 26.7% cases of chronic myeloid leukemia. A significant proportion of them showed early disease progression.<sup>14</sup>

The platelet count per se has shown significant correlation with thrombosis risk and various studies suggest that, in high risk patients,

It has been observed that in patients with marked

thrombocytosis and high thrombosis risk, lowering the platelet count to below  $400 \times 10^9/l$  may reduce the

incidence of thrombotic events; however, such clinical response may also be considered as a part of the overall effect of myelosuppression. Our patient was put on therapy for CML and is improving clinically. As has been reported in different studies that treatment for MPD (without using anticoagulant) thus lowering leukocyte count not only prevents the aggregation of leukemic cells and formation of thrombus this may also resolve the thrombus even without heparin therapy.<sup>15</sup> In the present case JAK 2 mutation and bone marrow biopsy were not performed initially. Whether this is a case of mixed myeloproliferative disorder or is a transformation of thrombocytopenia to CML is still not resolved. We have suggested him to repeat platelet count and JAK2 mutation analysis so that treatment can be tailored accordingly. It is suggested that patients with venous thrombosis who have even slightly raised white cell and platelet counts should be investigated thoroughly and MPD should be ruled out by doing cytogenetic/molecular genetic studies at the earliest.

## Conclusion

This patient did not present with hyperleukocytosis (which is usually a cause for thrombosis in CML) and after two years was diagnosed as a case of CML. He however had thrombocytosis at that time but was not evaluated for Thrombocytopenia. It is thus suggested that patients with history of thrombosis should be monitored and evaluated for MPD particularly if they show even slightly raised platelet count or leukocyte count.

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