

Splenic Infarct and Stroke in a Patient of Essential Thrombocythemia: Rare Clinical Scenario

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Abstract

Essential thrombocythemia (ET) is one of the myeloproliferative neoplasms characterised by thrombocytosis and megakaryocytic hyperplasia in the bone marrow. ET may be occasionally complicated by thrombo-hemorrhagic events. Small and medium vessel thrombosis is the most common. Infarction in the spleen in a patient with ET is a rare clinical scenario. Here we present a case of a patient with splenic infarct, where subsequent investigations led to the diagnosis of ET. She also had a history of cerebrovascular thrombosis in the past. Patient responded well with anticoagulation and cytoreductive therapy. Early diagnosis and prompt initiation of management is of pivotal importance to prevent further thrombotic episodes in ET. A physician needs to explore such possibility during the investigation of a case of splenic infarct.

Keywords: *Essential Thrombocythemia (ET); Myeloproliferative Neoplasms; Bone Marrow*

Introduction

Essential thrombocythemia (ET) is one of the myeloproliferative neoplasms characterised by thrombocytosis ($450 \times 10^9/L$ or more) and megakaryocytic hyperplasia in the bone marrow. Mutations in three important genes: Janus kinase 2 (JAK2V617F), Calreticulin (CALR), and Myeloproliferative leukemia virus oncogene (MPL) have been described with regard to ET. The symptoms of ET are quite variable, although mostly the patients are asymptomatic. However, ET may be complicated by thrombotic and/or hemorrhagic events, small and medium vessel thrombosis being the most common. ET may present with erythromelalgia, transient ischemic attack, myocardial infarction, deep vein thrombosis or pulmonary embolism [1]. Thrombosis in large vessels rarely occurs and there is limited evidence to guide management [1]. Patients with ET are also at an increased risk of progression to myelofibrosis or acute myeloid leukemia. Here, we present a case of a patient with essential thrombocythemia complicated by cerebrovascular thrombosis as well as splenic infarct.

Case Report

A 35 years old female presented in the emergency of a tertiary care hospital in North India with complaints of pain abdomen of 2 weeks duration, that had increased in severity in the last few days, prior to presentation. The pain was insidious in onset, gradually progressive, localised in the left upper abdomen. It was dull aching in character and moderate to severe in intensity. However, there was no history of radiation of pain, constipation, loose stools, vomiting, fever or passage of black colored stools. She had a history of cerebrovascular thrombosis one year back for which she was not compliant to medications that had been prescribed to her. There was no history of any other chronic illness.

On examination, she had a BMI of 22 kg/m². Her blood pressure was 130/80 mm of Hg and pulse rate was 80 beats per min with a regular rhythm. Her abdominal examination revealed massive splenomegaly which was enlarged 10 cm below left costal margin. It was firm in consistency having well defined margins and smooth surface with a palpable splenic notch. Further examination also revealed hepatomegaly 8 cm below right costal margin with a liver span of 18 cm.

In neurological examination, she had a right sided hemiparetic gait with a slurred speech. She had weakness in the right upper as well as lower limb with power 4/5 (Medical Research Council muscle strength grading system). The deep tendon reflexes in the right upper and lower limbs were exaggerated and the planter reflex was extensor in the right side.

Her complete hemogram revealed a hemoglobin of 11 g/dl and a total leukocyte count of 33000 cells/dl and 37000 cells/dl on two different occasions. The differential count revealed neutrophilic picture. Peripheral blood smear showed increased number of platelets with an absolute platelet count of 10 lac/cmm and 15 lac/cmm respectively. Blood biochemistries revealed normal renal as well as liver function tests with raised uric acid level of 10.2 mg/dl. Her blood sugar and thyroid profile were within normal range.

Ultrasonography examination of whole abdomen revealed an enlarged spleen measuring 20 cm approximately with normal echo texture and liver measuring 18 cm with normal echo texture. Following which, she had contrast enhanced CT of the abdomen and pelvis in arterial and venous phases. CT demonstrated hepatomegaly and massive splenomegaly with large non enhancing wedge shaped hyper dense area at mid pole of spleen – suggestive of splenic infarct (Figure 1). Non contrast CT head was done which revealed chronic infarct in left sided fronto-temporo-parietal region (Figure 2). To find cause of thrombocytosis, bone marrow aspiration and biopsy was done. It showed cellular marrow smears with increased myeloid: erythroid ratio. Megakaryocytes were increased and were seen in mature as well as immature forms. Myeloid cells were increased in number and were seen in all forms of maturation and differentiation. Bone marrow aspiration and biopsy was suggestive of chronic myeloproliferative disorder (Figure 3). Subsequently, JAK2V617F mutation was done which was positive and BCR-ABL was negative. A final diagnosis of essential thrombocythemia with splenic infarct was made. She was started on tablet Hydroxyurea 500 mg twice daily as a part of cytoreductive regimen. She was also kept on enoxaparin in addition to warfarin till the therapeutic range of INR was reached. Then, enoxaparin was stopped and the patient was discharged on the same dose of warfarin and Hydroxyurea and was advised for outpatient follow up.

Discussion

According to World Health Organisation, the diagnosis of ET can be made if the following major criteria are met: 1) platelet count > 450 × 10⁹/L; 2) increased numbers of enlarged and hyperlobated mature megakaryocytes in the bone marrow without left shift of neutrophil granulopoiesis or erythropoiesis and no more than grade 1 reticulin fibrosis; 3) not meeting criteria for other myeloproliferative neoplasms, myelodysplastic syndrome, leukemia, or other myeloid disorders; 4) presence of JAK2, CALR, or MPL mutation. Alternatively, ET may be diagnosed if the first three major criteria are met, and another clonal marker is identified or reactive thrombocytosis is excluded [2].

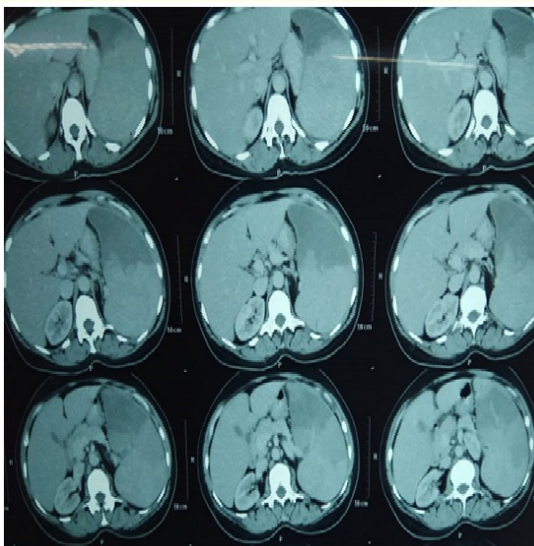


Figure 1: Contrast enhanced CT of upper abdomen revealing large wedge-shaped hypodense area in the spleen suggestive of infarct.

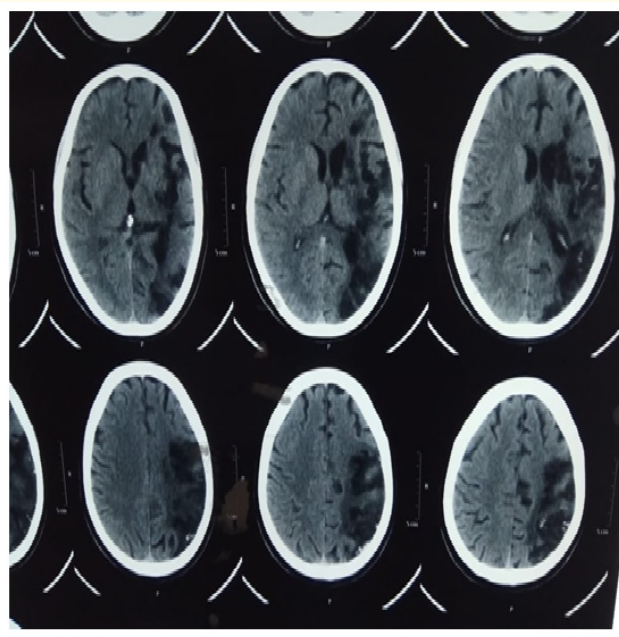


Figure 2: NCCT head showing chronic infarct in left parieto-temporo-frontal region.

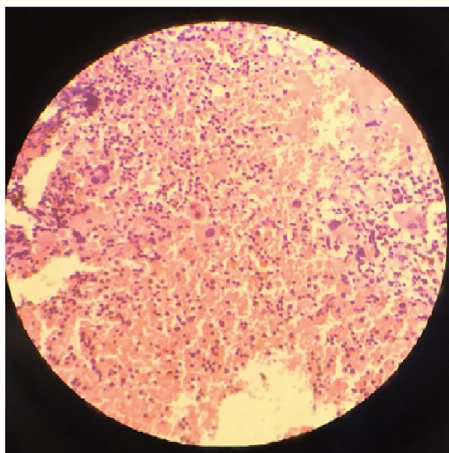


Figure 3: 400 X magnification showing increase in both mature and immature megakaryocytes.

In this case, presumptive clinical diagnosis of ET was considered based on thrombocytosis, increased megakaryocytes on bone marrow evaluation with history of cerebrovascular thrombosis. The characteristic morphology on bone marrow evaluation, absence of iron deficiency, infection or inflammatory disorders and positive JAK2V617F mutation confirmed the diagnosis of essential thrombocythemia.

ET is a disease that occurs in the presence of Janus kinase 2 (JAK2), Calreticulin (CALR) or myeloproliferative leukemia virus oncogene (MPL) mutation along with absence of any clonal or reactive causes of thrombocytosis [3]. The pathogenesis of ET is the overproduction of hematopoietic cells due to the mutations in the 'driver genes' of JAK2, CALR or MPL. These are evident in 50 - 60%, 25 - 30% and 3 - 5% patients of ET respectively. The mutations are responsible for their myeloproliferative effects. The single point mutation in JAK2 (change in amino acid from Valine to Phenylalanine at codon 617; JAK2V617F) leads to the gain of function and activation of intracellular signalling pathways associated with the receptors of hematopoietic cytokines: erythropoietin, thrombopoietin and granulocyte colony-stimulating factors [4]. CALR is usually involved in cellular proliferation, differentiation and apoptosis. However, MPL mutation is usually a point mutation and observed in 3 - 5% of ET patients. The detection of these mutations form an important tool towards diagnosis. Increased myeloproliferation results in an altered microvascular milieu in the body and is the cause for several thrombotic events despite the atherosclerotic and cardiovascular risk factors of the patient.

The patients of ET can have various presentations. In asymptomatic patients, thrombocytosis is an incidental finding on complete blood count. The most frequent symptoms are migraines, headache and dizziness [5]. Transient ischemic attacks, erythromelalgia and easy bruising are infrequent presentations. Its natural history can course into adverse cardiovascular events, bleeding as well as transformation to myelofibrosis and acute myeloid leukemia. The most common physical finding is splenomegaly.

The spontaneous activation and aggregation of hypersensitive platelets contribute to thrombosis in ET. Histopathologic evaluations of arterial thrombi in ET have revealed platelet-rich clots with abundant von Willebrand factor as well as less fibrin [6]. Thrombosis may occur despite normal platelet count, which emphasises the underlying microvascular circulation disturbances in ET. The thrombotic incidents at the time of diagnosis and during follow up the disease occur in rates of 10 - 29% and 8 - 31% respectively [7]. The incidence of thrombosis is 1.0 - 2.5 individuals per 100,000, and it increases with age, with most patients presenting between the ages of 50 and 60

[5]. Advanced age and previous cardiovascular events are risk factors for increased incidence of thrombosis. Thrombosis occurs in 20% of the cases followed by haemorrhage (10%) [5].

Several studies have reported cases of cerebro-vascular thrombosis, coronary artery thrombosis, hepatic vein thrombosis (Budd-chiari syndrome), splenic artery thrombosis as well as adrenal thrombosis as rare manifestations of the disease [7-11]. ET is also associated with adverse pregnancy outcomes like eclampsia, placental abruption, intrauterine growth retardation and still birth. Other complications of ET include splenomegaly due to increased viscosity of blood which may be associated with infarction, rupture, hemorrhage or abscess formation. High erythrocytes and thrombocytes can predispose to rupture of gastrointestinal ulcers and bleeding. ET often transforms to diseases like myelofibrosis, myelodysplastic syndrome and acute leukemia [12].

Splenic infarction is rare and can present with left upper quadrant pain or left lower chest pain. It may be associated with fever, chills, nausea, vomiting and pleuritic chest pain or left shoulder pain (Kehr sign) [13]. Primary causes of splenic infarcts are hematological disorders like: sickle cell hemoglobinopathies, leukemia, lymphomas, myelofibrosis, embolic disorders secondary to atrial fibrillation, endocarditis, prosthetic mitral valve, left ventricular thrombus; collagen vascular disorders like systemic lupus erythematosus, polyarteritis nodosa; infections (infective mononucleosis, salmonellosis, plasmodium falciparum); and trauma. Spleen is supplied by splenic artery (branch of coeliac artery) and the short gastric artery (branch of left gastroepiploic artery). Arterial supply is segmental within the spleen, hence occlusion of secondary branches result in a wedge-shaped infarct [9]. Very few cases of splenic infarct secondary to ET have been reported till date. In our case the patient presented with splenic infarct and subsequent investigations led to the diagnosis of ET. The cerebrovascular thrombotic episode which had occurred previously was also hypothesised to be the result of similar hypercoagulable milieu in the body, which was not diagnosed then.

Various studies establish the association between ischemic strokes and ET. The incidence is 0.25 - 0.5% [10]. In a series of 148 patients with an average follow up of six years, cerebral ischemia was the most common ischemic manifestation in ET patients [14]. Age and atherosclerotic risk factors predispose to this condition. In a series of 13 acute cerebrovascular events in ET, the most frequent stroke subtype was water-shed infarcts even in the absence of large artery stenosis [10]. Multiple factors like platelet activation, increased turnover, endothelial activation, alteration and inhibition of coagulation contribute to the prothrombotic states in ET. It may also induce arteriosclerosis because of platelet activation [15]. Early diagnosis of ET and strict management of vascular risk factors is essential to prevent further such occurrences.

Current treatment recommendations in ET classify patients in 4 categories: Very low-risk disease (no history of thrombosis, age < 60 years, JAK2 unmutated), Low-risk disease (no history of thrombosis, age < 60 years, JAK2 mutated), Intermediate risk disease (no history of thrombosis, age > 60 years, JAK2 unmutated) and High risk disease (history of thrombosis or age > 60 years with JAK2 mutation). Once daily aspirin is recommended in very low risk patients with cardiovascular risk factors, twice daily aspirin is recommended in low risk patients with cardiovascular risk factors. Hydroxyurea and once daily aspirin is recommended in intermediate risk patients with cardiovascular risk factors. In high risk disease, hydroxyurea with systemic anticoagulation is preferred in patients having history of thrombosis [2]. Additional platelet directed therapies like clopidogrel (irreversible ADP receptor P2Y₁₂ inhibitor), cilostazol (phosphodiesterase type 3 inhibitor) have been tried in studies with various results [1]. Antiplatelet therapy in combination with cytoreductive treatment is more effective and results in 50% reduction in risk of recurrent thrombosis [10].

There is no specific guidelines for management of splenic infarcts due to the rarity of the case. Medical management with supportive medications like NSAIDs have been used in uncomplicated cases. On the other hand, surgical procedure or splenectomy has been used in the presence of complications like abscess, sepsis, persistence of symptoms [12]. In our case, the patient was managed with antiplatelets and anticoagulation and recovered significantly during follow up.

Conclusion

Splenic infarction is a rare and life threatening complication of ET. A physician needs to explore such possibility for early diagnosis and treatment. The majority of patients can be managed conservatively, but regular follow up and assessment of risk factors is of pivotal importance to prevent recurrences.

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