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Review Article

Essential thrombocytosis: review of literature with a rare presentation of cerebral thrombosis treated with endovascular therapy

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ABSTRACT

Essential thrombocytosis (ET) is a clonal hematopoietic stem cell disorder. Clinically there is an over-production of platelets without a definable cause. ET is a myeloproliferative neoplasm (MPN). It has an incidence of 1 to 2 per 100,000 population and a distinct female predominance. Once considered a disease of the elderly and responsible for significant morbidity due to haemorrhage or thrombosis, it is now clear that ET can occur at any age in adults and often without symptoms or disturbances of hemostasis. ET can cause both thrombosis or haemorrhage and carries a risk of acute leukemic transformation. Being an MPN, in some cases, polycythemia vera (PV) or primary myelofibrosis (PMF) can present as ET. Though the average life expectancy only slightly deviates from the standard expected for age-matched individuals, a thorough understanding of its etiopathogenesis, clinical presentation, complication and management can make a world of difference to patients. Thrombosis is one such complication that has a significant impact on the mortality and morbidity of ET. We proposed using endovascular therapy (EVT) as a treatment modality for cerebral venous sinus thrombosis.

Keywords: Essential thrombocytosis, Hydroxyurea, Myeloproliferative neoplasm, Endovascular therapy, Cerebral venous sinus thrombosis

INTRODUCTION

ET was first recognized in 1934. It was classified as a myeloproliferative neoplasm by Damesheck in 1951.[1] The revised 2016 WHO classification of hematopoietic tumours distinguishes MPNs as:[2] chronic myeloid leukaemia, BCR-ABL1+; chronic neutrophilic leukaemia, often CSF3R mutated; chronic eosinophilic leukaemia, not otherwise specified; MPN, unclassifiable; PV; ET and PMF.

Other terminologies for ET include essential thrombocythemia, idiopathic thrombocytosis, primary thrombocytosis and hemorrhagic thrombocythemia.[3] ET being an MPN is characterised by clonal stem cell myeloproliferation resulting in thrombocytosis. This clonal myeloproliferation is driven by mutations in (Janus associated kinases) JAK2, calreticulin (CALR) and myeloproliferative leukaemia (MPL) mutations (the so-called driver mutations).[4] These mutations are also seen in PV and PMF. ET is characterised by thrombocytosis with the presence of megakaryocytic hyperplasia in the bone marrow. Due to thrombocytosis, there is a risk of vascular events (thrombosis and haemorrhage) and sometimes the conversion to a blast phase of myelofibrosis.

Genetics

JAK2V617F is the most common mutation seen in ET, occurring at a frequency of 55%.[5] Calreticulin (CALR:

19p13.2) mutations are observed at a frequency of 15-

(Ca2+) binding protein chaperone primarily localised in the endoplasmic reticulum.[6-8] MPL (virus oncogene; 1p34) mutations occur in approximately 4% of ET patients. MPLS505 N is a germ-line (hereditary thrombocythemia) and somatic (ET) mutation.[9-11] Hereditary thrombocytosis has also been reported with germ-line JAK2 mutation (JAK2V617I). It is associated with vascular events but not fibrotic/leukemic progression.[12] The presence of increased allele burden of JAK2V617F does not affect survival or leukemic transformation in ET. In ET, the presence of JAK2V617F is associated with an increased risk of thrombosis and a lower risk of post ET myelofibrosis.[13] In ET, mutant CALR (versus JAK2) is associated with younger age, male sex, higher platelet count, lower haemoglobin levels, lower leukocyte counts and lower frequency of thrombosis; type 2 versus type 1 CALR mutations are associated with greater platelet count.[14] MPL mutations have no associations with survival or leukaemic transformation.[11,15] 20% of patients with ET might be triple-negative (negative for all three mutations). In the absence of these mutations, the possibility of chronic

24% in ET patients. CALR is multi-functional calcium

myeloid leukemia (CML) should be excluded by BCR-ABL1 mutation screening.[5]

Clinical features

Clinically, ET is often identified incidentally when a platelet count is obtained during a routine medical evaluation. Occasionally, a review of previous blood counts will reveal that an elevated platelet count was present but overlooked for many years. No symptoms or signs are specific for ET, but these patients can have haemorrhagic and thrombotic tendencies expressed as easy bruising for the former and microvascular occlusive events for the latter such as erythromelalgia, ocular migraine or a TIA. Physical examination is generally unremarkable except occasionally for mild splenomegaly.[16] Significant splenomegaly is indicative of another MPN, in particular PV, PMF or CML. In a COHORT of 253 ET patients in the study by Accurso et al between June 1993 and January 2020, the frequency of complaints was as follows (Figure 1).[17]

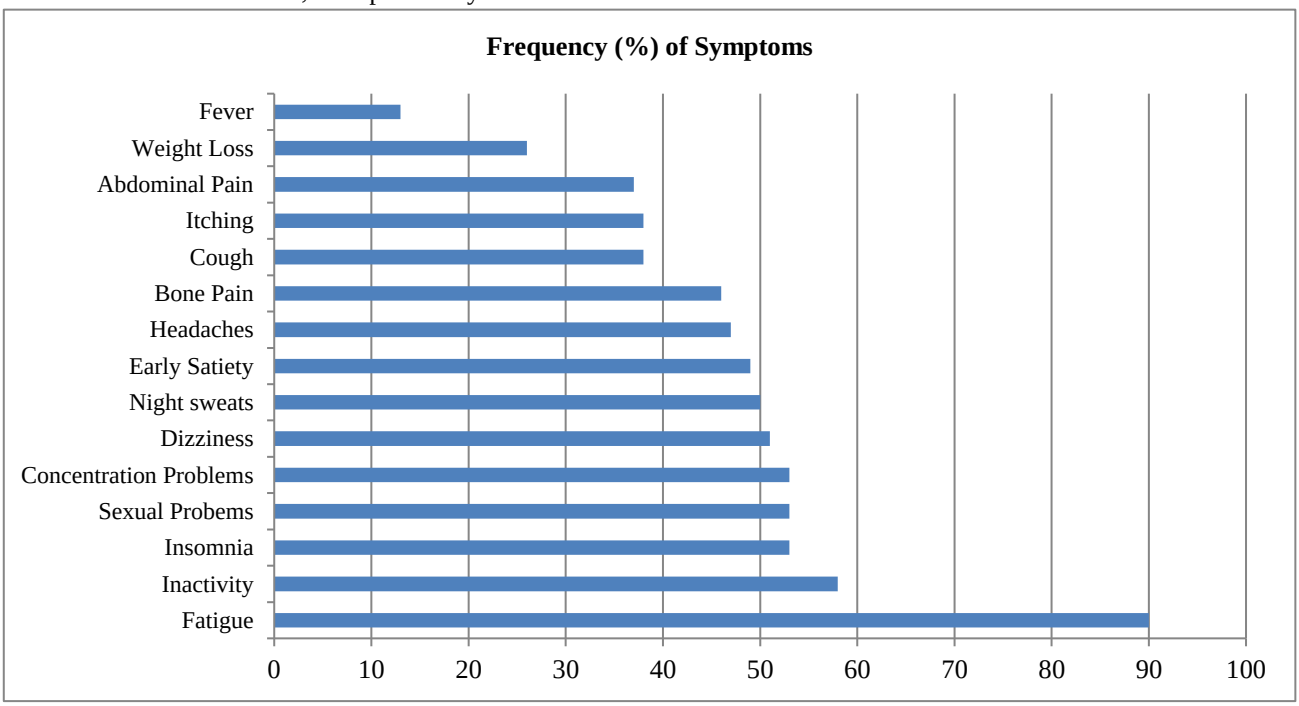

Figure 1: Frequency of complaints.[17]

The symptoms are fatigue (90%), inactivity (58%), numbness (58%), insonnia (53%), sexual problem (53%), concentration problem (53%), dizzness (51%), night sweats (50%), early satiety (49%), headache (47%), bone pain (46%), cough (38%), itching (38%), abdominal pain (37%), weight loss (26%) and fever (13%).

Laboratory features

Mild neutrophilic leukocytosis is not uncommon, but anaemia is unusual. The blood smear shows a bountiful number of platelets, some of which may be very large. A

pseudohyperkalemia may develop as a test tube artefact and prevent the accurate measurement of serum potassium due to the release of platelet potassium upon blood clotting. This finding is not associated with electrocardiographic abnormalities. The prothrombin and partial thromboplastin times are typical. However, prolonged bleeding time and impaired platelet aggregation can be present. Marrow biopsy usually reveals megakaryocyte hypertrophy and hyperplasia as well as an overall increase in marrow cellularity. The elevated platelet count may hinder marrow aspiration.[3]

Diagnosis

Thrombocytosis is encountered in a wide variety of clinical disorders, in many of which inflammatory cytokine production is increased. The absolute level of the platelet count is not a valuable diagnostic aid for distinguishing between clonal and benign causes of thrombocytosis.[3]

Causes of this reactive thrombosis include tissue inflammation, e.g. collagen vascular disease, inflammatory bowel disease; haemorrhage; malignancy; postsplenectomy or hyposplenism; iron-deficiency anaemia; rebound phenomenon like correction of vitamin B12 or folate deficiency, post-ethanol abuse; familial; infection; surgery; myelodysplastic disorders like 5q-syndrome, idiopathic refractory sideroblastic anaemia and hemolysis.

Currently, ET diagnosis is according to 2016 WHO criteria and based on a composite assessment of clinical and laboratory features.[2]

Major criteria

The major criterias are platelets ≥4,50,000 /μl; bone marrow megakaryocyte proliferation and loose clusters; not meeting WHO criteria for other myeloid neoplasms and JAK2/CALR/MPL mutation.

Minor criterion

The minor criterion was other clonal markers present or no evidence of reactive thrombocytosis.

Diagnosis requires all four major criteria or the first three majors and the minor criterion.

Risk factors

Risk factors for overall survival are advanced age, thrombosis history, leukocytosis and anaemia.

Risks for leukemia-free survival are prefibrotic PMF morphology, thrombosis and extreme thrombocytosis (platelets >10,00,000 /μl).

Risk factors for fibrotic transformation are prefibrotic PMF morphology, advanced age and anaemia, while JAK2V617F is associated with a lower risk of fibrotic transformations.[5]

Male sex is an independent risk factor for overall survival in ET.[18]

Risk stratification includes four categories: very low risk (age ≤60 years, no history of thrombosis, JAK2 wild-type); low risk (age ≤60 years, no history of thrombosis, JAK2 mutated); intermediate risk (age >60 years, no history of thrombosis, JAK2 wild-type) and high risk (history of thrombosis or age >60 years with JAK2 mutation).

Treatment recommendations[5]

Very low-risk disease

No cardiovascular risk factors: keep under observation. No intervention is needed.

Cardiovascular risk factors present. Once daily aspirin.

Low-risk disease

No cardiovascular risk factors: once or twice daily aspirin (depending on symptoms)

Cardiovascular risk factors present: twice daily aspirin

Intermediate risk disease

No cardiovascular risk factors: once daily aspirin (hydroxyurea is optional)

Cardiovascular risk factors present: once daily aspirin in addition to hydroxyurea

High-risk disease

History of arterial thrombosis at any age: twice daily aspirin in addition to hydroxyurea

History of venous thrombosis at any age: hydroxyurea in addition to systemic anticoagulation

Other treatment options

Anagrelide

Phosphodiesterase 3 (PDE3) inhibitor inhibits nucleotide PDE and the release of arachidonic acid from phospholipase A2; also reduces platelet production by disrupting the maturation phase of megakaryocytes.

Ruxolitinib

Inhibits the JAKs, JAK1 and JAK2, which mediate the signaling of several cytokines and growth factors necessary for hematopoiesis and immune function.

Pipobroman

It is an antineoplastic agent. It is a piperazine derivative with a chemical structure resembling several alkylating agents. Pipobroman has well documented clinical activity against ET and PV. Its mechanism of action is uncertain,

but pipobroman is thought to alkylate DNA leading to disruption of DNA synthesis and eventual cell death.

Busulfan

Alkylating agent; interferes with DNA replication and RNA transcription; cross-links DNA strands; has little immunosuppressive activity; affects myeloid cells more than lymphoid cells; very toxic to hematopoietic stem cells.

Interferon-α

Interferon-alpha (IFN) inhibits the growth of megakaryocytic progenitors in normal hematopoiesis and patients with ET, leading to reduced peripheral platelet counts.[19]

Complications

Thrombosis is the most common cause of mortality and morbidity in patients with essential thrombocytosis, can occur in 20% of the patients. It can occur in the arterial or venous circulation. Haemorrhage is reported in 10%. ET is also associated with pregnancy complications like eclampsia, placental abruption, intrauterine growth retardation and stillbirth.[1]

Prognosis

The median survival for ET is approximately 20 years. For patients younger than age 60 years, the expected survival was 33 years. In the study by Tefferi et al life-expectancy in ET was inferior to that of the age- and sex-matched US population and that survival in ET was superior to that of PV, regardless of the mutational status.[20]

Case report

A 46 year old male patient presented to the medical OPD with the complaint of raised platelet count. After a thorough history taking and physical examination, it was revealed that the patient went to his local doctor with the complaint of generalised weakness of 3 months duration, for which he underwent routine blood tests. It was then revealed that his platelet count was elevated to 10,43,000/µl. He was referred to us for further management.

There was no history of hypertension, diabetes mellitus, smoking or other cardiovascular risk factors. He had no prior knowledge of his elevated platelet counts. He also expressed periodic redness and burning of palms and soles on subsequent questioning, occasional headaches, and visual disturbances, no history of bruising. There was no other relevant documentation.

His physical examination was unremarkable. His initial vital signs were pulse rate 84 beats per minute, respiratory rate 17 breaths per minute, temperature 98.6 °F, oxygen saturation 98% on room air and blood pressure 123/84 mmHg. Examination of the respiratory system revealed bilateral normal vesicular breath sounds. Cardiovascular system examination revealed normal first and second sounds with no murmurs or clicks. The abdomen was soft without any evidence of tenderness or organomegaly and bowel sounds were present.

Serum biochemical test results were unremarkable. Laboratory investigations showed haemoglobin 12 gm/dl, total leucocyte count 10,400 cells/µl and platelet count 10,55,000/µl. A peripheral blood smear examination revealed thrombocytosis with giant platelets. Serum iron studies were within normal limits. Bone marrow aspirate and biopsy showed hypercellular marrow with trilineage haematopoiesis with increased megakaryocytes in clusters with matured cytoplasm, containing multilobulated nuclei, features favouring ET. Bone marrow iron stores were regular. Mutational detection for JAK2V617F, CALR and MPL was negative (triple-negative).

The patient was classified as low risk and low dose aspirin (75 mg) was started to ease his vasomotor symptoms. The patient was counselled regarding the nature of the disease and his prognosis. There was a gradual improvement in his symptoms. He was in regular follow up and there were no other complaints. However, seven months after his initial presentation to us, the patient was brought to the emergency department with a severe headache, visual blurring of 4 days duration and seizures with altered sensorium of 3 hours duration.

On examination, the patient was drowsy and disoriented. His vital were pulse rate 106 beats per minute, respiratory rate 24 breaths per minute, temperature 100.6 °F, oxygen saturation 97% on room air and blood pressure 122/87 mmHg. Glasgow coma scale (GCS) score was 8. Routine blood investigations were sent. A computed tomography (CT) scan and CT venogram were done. The platelet count was 12,43,000/µl. CT venogram showed thrombosis of the superior sagittal sinus (SSS). Antiepileptics were started. After obtaining informed consent from his family, endovascular therapy with combined thromboaspiration and stent retriever (Solumbra technique) was initiated.

Procedure

Patient was on the angiographic table. A 6F short sheath was inserted into the right femoral artery in the groin. A cerebral angiogram was taken and arterial, capillary and venous phases were obtained, which helped us reconfirm the site and the extent of thrombosis. A 7F short sheath was placed into the internal jugular vein in the neck. TA of the SSS was done with CAT6 catheter (Stryker Neuro-vascular). A check angiogram revealed residual thrombus. A REBARR 27 catheter was navigated with a Synchro 0.014 wire and the thrombosed part of the

sinuses was crossed. A 6×30 mm Solitaire stent retriever was deployed into the thrombus. It was kept in place for 3 to 5 min. After the clot was adequately engaged, the stent retriever was retrieved along with the clot. A check angiogram for any residual thrombus was done. The procedure was repeated till a complete recanalisation was achieved.

Repeat CT angiogram 24 hours after the procedure showed good persistent revascularisation. Clinical improvement was noticed in the next few days and his modified Rankin score (mRS) at the time of discharge was 0. His discharge medication was dabigatran 150 mg twice daily, levetiracetam 500 mg twice daily and hydroxyurea 500 mg twice daily. His platelet count at the end of 2 months was 3,59,000/µl. There was no recurrence of any similar symptoms and the medication is tolerated well.

DISCUSSION

ET is an indolent disease, but it is not curable; however, patients should be aware that they must be compliant with recommended medications to prevent complications from the disease. Patients need to follow up with their health care providers for close monitoring.

Low-dose aspirin therapy effectively alleviates vasomotor (microvascular) disturbances associated with ET.21 ET's vasomotor symptoms constitute lightheadedness, headaches, transient ocular or neurologic disturbances, tinnitus, chest discomfort, paresthesias or erythromelalgia. These symptoms may stem from small vessel-based abnormal platelet-endothelial interactions.[22] Aspirin therapy is also considered adequate and potentially helpful in preventing complications during pregnancy, especially in JAK2V617F-positive cases.[23-25]

Regarding aspirin therapy in ET, a recent report suggested that twice-daily aspirin may work better than once daily dose in some instances.[26] In the presence of aspirin-resistant symptoms, it is reasonable to utilise a twice-daily rather than once-daily regimen of low dose aspirin or alternative anti-platelet agents such as clopidogrel (75 mg/d) alone or in combination with aspirin.[27] Patients should be closely monitored for drug side effects. One might also consider platelet-lowering therapy (e.g. hydroxyurea) in aspirin-refractory cases, but the target platelet count should be the level at which relief of symptoms was observed and not necessarily 4,00,000/µl. It was reasonable to use twice-daily aspirin use in low-risk patients with JAK2-mutations and cardiovascular risk factors.

In addition to low-dose aspirin, hydroxyurea is the first-line cytoreductive drug of choice in order to minimise their risk of thrombosis (starting dose 500 mg BID) in high-risk patients with ET. The dose was titrated to keep platelet counts in the normal range. However, this recommended platelet target was not based on controlled evidence. ET patients who were either resistant or intolerant to hydroxyurea were effectively managed with second-line drugs, INF-α (pegylated preparations preferred) or busulfan. The use of INF-α was preferred in patients younger than age 65 years. Busulfan was preferred in the older age group, although there was no controlled evidence to support or refute such a strategy. Busulfan was started at 2-4 mg/d and withheld when platelets <2,00,000/µl or WBC <3,000/µl and the dose were reduced to 2 mg/d when treatment was restarted after withholding. Subcutaneous pegylated IFN-α was started at 45 mcg once a week and titrate up to 180 mcg once a week if tolerated well.

In the study by Cortelazzo et al the incidences of thrombotic complications were 3.6% for hydroxyurea and 24% for non-hydroxyurea groups.[28] Two randomised studies in ET compared hydroxyurea with anagrelide. In the first study by Harrison et al high-risk patients were given low-dose aspirin with either anagrelide or hydroxyurea.[29] Hydroxyurea was better at reducing the risk of arterial thrombosis, bleeding and fibrotic progression. Anagrelide was better at curtailing venous thrombosis. However, adverse dropout rates were significantly higher in the anagrelide group. In the second study by Gisslinger et al anagrelide was compared with hydroxyurea in high-risk ET patients.[30] There were no significant differences between the anagrelide and hydroxyurea group regarding incidences of major arterial and venous thrombosis, severe bleeding events, minor arterial and venous thrombosis and minor bleeding events or discontinuation rates.

Ruxolitinib (JAK1/2 inhibitor) was most recently compared with the best available therapy in hydroxyurea unresponsive/intolerant high-risk ET in a randomised phase-2 study.[31] The 1-year complete response rates were similar in the 2 study arms as were the 2-year rates of thrombosis, haemorrhage and leukaemic/fibrotic transformation.

In the retrospective study of 164 patients with ET treated with pipobroman as the first-line therapy and followed up for a median of 100 months, acute myeloid leukaemia occurred in 5.5% of the cases.[32] In another study of 33 ET patients <50 years of age treated with pipobroman and followed for a median of almost 16 years, complete remission was seen in 94%. One patient (3%) developed AML. No patient experienced thrombotic complications.[33]

In a long-term study of 36 ET patients above age 60, treated with busulfan, no instances of malignancies were reported after a median follow up of 72 months.[34]

IFN-α can control thrombocytosis in the majority of patients with ET. Recent studies of pegylated INF-α in ET reported hematologic remissions of ~80%, accompanied by decreases in the JAK2V617F allele

burden. Seventy-seven cases were evaluated after a median follow up of 21 months and 76% of patients with ET achieved complete hematologic remission, mainly in the first three months. However, side effects were reported in 96% of the patients and 22% had to discontinue the treatment.[35] IFN therapy is also associated with a significant reduction in mutant CALR allele burden in ET.[36]

In the study of 891 ET patients by Carobbio et al 109 (12%) patients developed arterial (n=79) or venous (n=37) thrombosis.[37] The predictors for arterial thrombosis include age >60 years, prior history of thrombosis, cardiovascular risk factors including tobacco use, diabetes mellitus or hypertension, leukocytosis (>11,000 /µl) and presence of JAK2V617F.[38] In contrast, only the male gender predicted venous thrombosis. Interestingly, a platelet count of more than 10,00,000 /µl was associated with a lower risk of arterial thrombosis. Mutant CALR (versus JAK2) was associated with a lower incidence of thrombosis without affecting the international prognostic scoring system for thrombosis in ET.

Thrombosis can occur in the cerebral, coronary, hepatic vessels. Venous thromboses in atypical sites were more frequent than in the general population, especially involving splanchnic (SVT) or cerebral veins.[39]

Cerebral venous sinus thrombosis (CVST) is a rare and underreported manifestation of thrombosis with an incidence that varies with the studies. Among adults, the annual incidence of CVST was 2 to 5 cases per million population.[40,41] There was no definitive data regarding India as there were no multi-center hospital-based studies, but it was estimated to be higher than the average global incidence.[42] The management of CVST had always been complex because of the variety of underlying risk factors and the absence of a standardised treatment approach. Given the diversity of causes and presenting scenarios, CVST may commonly be encountered by neurologists, neurosurgeons, emergency physicians, internists, oncologists, haematologists, obstetricians, paediatricians and family practitioners. Thrombus formation in the cerebral venous circulation leads to increased hydrostatic pressure in the veins and capillaries upstream of the occlusion. Suppose the venous pressure increased more than the compensation capacity, blood-brain barrier disruption, extravasation of fluids into the cerebral parenchyma and consequent localised oedema can occur. In vasogenic oedema, the perfusion pressure was not usually reduced and therefore irreversible brain tissue damage was unlikely. The peculiarity of venous occlusion was reducing cerebrospinal fluid (CSF) reabsorption by reducing CSF access to the arachnoidal Pacchionian granulations, leading to raised intracranial tension. Prompt reestablishment of the venous flow by reducing the clot burden can mitigate these disastrous sequelae and improved the outcomes.[43]

Endovascular therapy was such an intervention that allowed for excellent and rapid recanalisation that improved the overall neurological outcomes. Liao et al endovascular mechanical thrombectomy and on-site chemical thrombolysis yielded mixed results in a retrospective single centre study, demonstrating improvement in 78.57% of patients.[44] The study by Dmytriw et al showed recanalisation rates of 61%.[45] The early initiation of ET can increased the success rates (while the clots remained in the acute phase composition, which was far more easily resolvable).[46] We did not employ catheter-directed therapy during the acute presentation due to the fear of haemorrhage.

CONCLUSION

Literature and clinical experience show that ET is an MPN with a relatively benign prognosis, with overall survival appearing slightly lower than that of the age-matched healthy general population.

The mutational status and the thrombotic risk critically influence therapeutic choices. Moreover, the introduction of very advanced molecular biology techniques has dramatically improved the under-standing of pathogenesis and the ability to diagnose and estimate prognosis.

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