Case study

An Unusual Cause of Bilateral Stroke

ABSTRACT

Background: Essential Thrombocythemia is one of the myeloproliferative disorders characterised by elevated platelet counts leading to an increased tendency for vessel thrombosis and hemorrhage affecting various organ systems. It is most common in the elderly but can occur at any age. The cerebral circulation is one of the systems affected and acute ischaemic stroke is a rare but described presentation of this disorder. This is a major cause of morbidity and mortality in these patients.

Objective: To describe a case of acute ischaemic stroke in a patient who was subsequently diagnosed as Essential Thrombocythemia.

Presentation of Case: We describe here a case of a 74 year old male who presented with acute ischaemic stroke and left hemiparesis. Investigations revealed high platelet counts and genetic analysis was positive for calr mutation seen in Essential Thrombocythemia. He was started on treatment for stroke along with cytoreductive therapy with hydroxyurea with improvement in symptoms. Through this report, we wish to highlight the importance of early identification and treatment of this uncommon cause of stroke in the elderly.

Key Words

Essential Thrombocythemia, Stroke, Hemiparesis

Key Message

Essential thrombocythemia is a rare but important cause of arterial thrombosis presenting with stroke. A high index of suspicion must be kept in all stroke patients with high platelet counts. Genetic testing can help diagnose and manage the condition.

ABBREVIATIONS

ET- Essential Thrombocythemia

MCA- Middle Cerebral Artery

ACA-Anterior Cerebral artery

PCA-Posterior Cerebral Artery

CALR- Calreticulin

DWI/ADC- Diffusion Weighted Imaging/Apparent Diffusion Coefficient

FLAIR-Fluid Attenuated Inversion Recovery

JAK2-Janus Kinase 2

MPL-Myeloproliferative Leukemia Virus

INTRODUCTION:

Essential Thrombocythemia is one of the myeloproliferative neoplasms classified in 1951 by Damesheck [1] . It has a prevalence in the general population of around 30/100,000. The median age at diagnosis of symptoms is around 65 to 70 years, but the disease may

occur at all ages. The condition is more common in females at a ratio of 2:1 .Essential Thrombocythemia is characterized by thrombocytosis with bone marrow involvement showing megakaryocytic hyperplasia. The high platelet counts causes a predisposition to vascular occlusive events involving multiple circulations and also hemorrhages. It is one of the rare causes of stroke in patients above sixty years[2]. We present here an unusual case of a elderly gentleman presenting with bilateral hemispherical stroke and subsequently diagnosed to have essential thrombocythemia.

CASE REPORT:

This 74 -year- old male patient with no comorbidities, presented to the emergency with a one day history of sudden onset of weakness initially in left lower limb followed a few hours later by loss of speech and right upper and lower limb weakness. Clinical examination showed motor aphasia , right hemiparesis and left lower limb weakness . Vitals were within normal limits and he was conscious and oriented. Magnetic resonance imaging scan of the brain showed multiple infarcts in the left middle cerebral artery and right middle cerebral/anterior cerebral artery watershed territories[figure 1]. Magnetic resonance angiogram imaging showed thrombotic occlusion of bilateral distal middle cerebral artery m1 segments[figure 2].

Blood investigations revealed elevated platelet counts -11,75000/mm3(normal range 150000-450000/mm3) with normal hemoglobin(13 grams/dl), total counts(7000/mm$^{3)}$, packed cell volumes , serum iron and erythrocyte sedimentation rate(20mm/hr). Anti nuclear antibody and antiphospholipid antibodies were negative in blood. Serum homocysteine, vitamin b12 and folic acid levels were within normal limits. Hematology opinion was taken for the

elevated platelet counts and the possibility of a myeloproliferative disorder like Essential Thrombocythemia was proposed .A bone marrow examination was suggested for confirmation but the family of the patient declined providing consent for the procedure. Genetic testing for myeloproliferative neoplasm gene alterations in peripheral blood was sent. The results revealed a 5 bp insertion in exon 9 of calr(calreticulin) gene which is one of the mutations responsible for essential thrombocythemia.

He was started on low molecular weight heparin along with antiplatelet agents, statins and anticonvulsants. He was also given physiotherapy , speech therapy and rehabilitation. After consultation with the hematology team, hydroxyurea was started in view of raised platelet counts. After physiotherapy, there was improvement in speech and motor power .Repeat platelet counts showed reduction in counts to 4,50000/mm3. He was discharged with regular follow up in both neurology and hematology departments. At follow up, he had improvement in motor power and also speech.

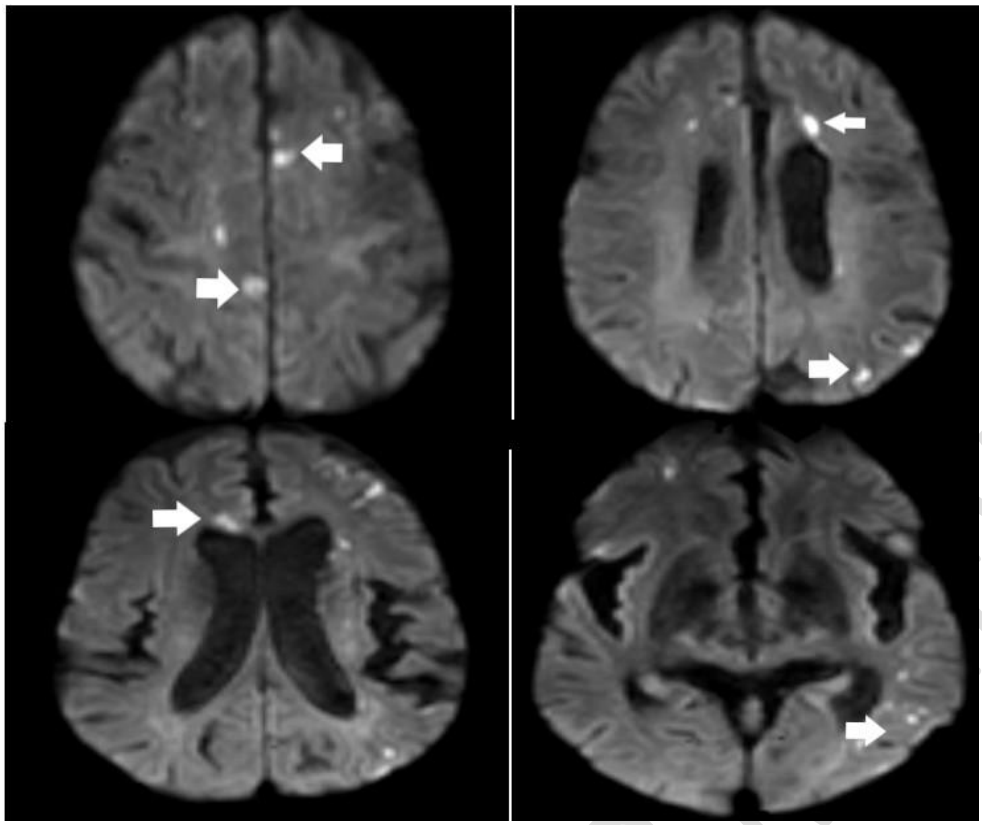

Figure 1 -Diffusion weighted images on mri scan showing scattered areas of diffusion restriction(white arrows) involving both cerebral hemispheres representing multiple infarcts in both anterior cerebral artery and middle cerebral artery territories

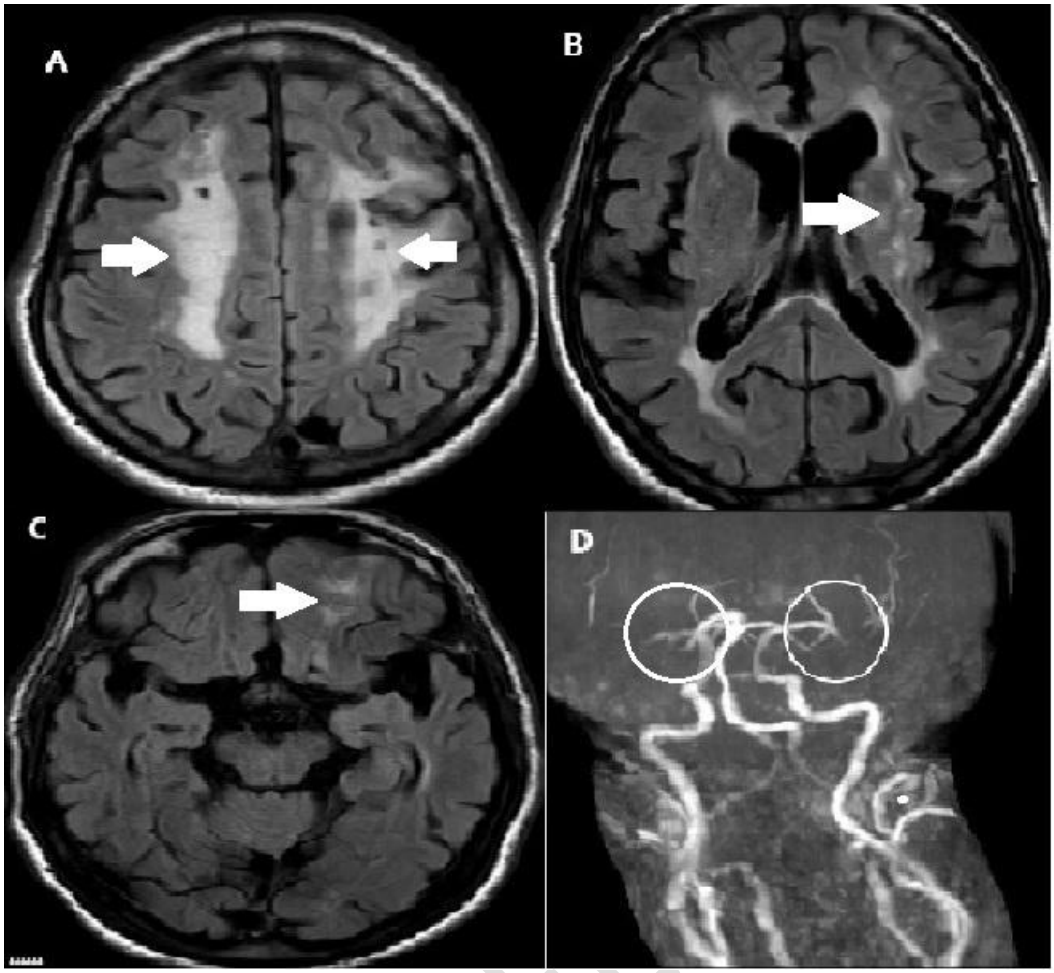

Figure 2 – A,B,C. Fluid attenuated inversion recovery(flair) sequences showing multiple ischaemic changes(white arrows) involving the bilateral frontal cortical periventricular areas(A), left perisylvian areas(B), left medial frontal subcortical areas(C) D. Magnetic resonance angiogram showing occlusion of bilateral distal middle cerebral artery m1 segment (white circles)

DISCUSSION

Essential Thromocythemia is a chronic myeloproliferative disorder in which sustained megakaryocyte proliferation leads to an increase in the number of circulating platelets in the bloodstream. Multiple genetic mutations are seen in this condition of which mutations in jak2(janus kinase 2), calr, or mpl(myeloproliferative leukemia virus) genes are the three main ones seen in approximately 90% of patients[3] . Jak 2 mutations are the most commonly seen comprising upto eighty percent. Patients with calr mutations are the second commonest ranging upto ten percent. These patients show a different phenotype in the form of higher platelet counts, lower hemoglobin values and lower thrombotic risk compared to the jak mutation patients[4]. Multiple mutation subtypes have been identified in calr mutation patients-especially types 1 and 2. Of these, the type 1 mutation variants have a higher risk of malignant transformation while type 2 has a benign course[5]. Also, patients with the calr mutation had a significantly higher associated platelet count as compared to the jak mutation patients. But the risk of thrombotic events was significantly lower in these patients[6]. This reinforces the theory that platelet activation and wbc counts may be more relevant to risk of thrombosis in these patients.

Clinical features most commonly include constitutional symptoms , thrombosis and hemorrhagic events[7]. Venous thrombosis is known to occur in the cerebral veins and also atypical sites like hepatic and portal veins. Pulmonary embolism is also well described in some cases. Arterial thrombosis can affect medium and large vessels predisposing to strokes and transient ischaemic attacks . Headache is the main presenting neurological symptom seen but seizures and visual blurring can also be seen. Symptoms can involve the cerebral, coronary and the peripheral vasculature. Large vessel thrombosis is a

major cause of morbidity and mortality here. Small vessels can also be affected causing transient occlusive thrombosis in the end-arterial circulation of various organs . One of the commonest symptoms seen is aspirin sensitive erythromelalgia, where we get burning in the extremities accompanied by toe ulcers. This may be accompanied by colour changes in the feet. In extreme cases, digital gangrene can also be a complication.

Bleeding manifestations involve the skin and can include epistaxis, gum bleeding, skin hematomas and ecchymoses. Bleeding manifestations are directly linked to the highest platelet counts and is due to an acquired Von Willebrand's disease that is caused by proteolytic reduction of Von Willebrand Factor (VWF) multimers. Aspirin may unmask a latent bleeding disorder in these patients , leading to various complications. It should be used with caution in patients with high platelet counts. Diagnosis is on the basis of blood picture, bone marrow biopsy and genetic testing .In our patient, diagnosis was made according to the british guidelines with sustained platelet count ≥4.5 lakhs, mutation in the calr gene and no other myeloid malignancy[8].

Treatment options are based on the risk stratification of these patients. High risk features involve increasing age, previous risk of bleeding or thrombosis and higher platelet counts.

Younger patients with no co morbidities and lower platelet counts are at a lower risk. Patients with age between 40 and 60 years and platelet counts lying between 10 and 15 lakhs /cu mm are designated to be at an intermediate risk. Treatment involves the use of aspirin to prevent thrombotic events and cytoreductive therapy with hydroxyurea or anagrelide[9]. Low dose aspirin has been known to reduce the risk of thrombotic and vaso occlusive manifestations. However, the use may be risky in older patients with very high platelet counts due to risk of bleeding.

Cytoreductive therapy with Hydroxyurea has been reported to reduce platelet counts and also the overall risk of vessel thrombosis. Mechanism of action in Hydroxyurea includes inhibition of DNA synthesis by blocking the ribonucleoside reductase activity .Alternative drugs include Anagrelide and interferon alpha. Pipobroman and Busulphan have also been recently explored in these patients. Options in resistant patients include the telomerase inhibitor Imetelstat and the monoclonal antibody Ruxolitinib[10] .Compared to the other disorders, ET has a relatively good prognosis with an expected survival of 18 to 19 years from the time of diagnosis as compared to 13.5 years in Polycythemia Vera and 5.9 years in Primary Myelofibrosis. The overall risk of blast transformation is lower in ET contributing to the better outcomes.

Our patient had arterial thrombosis involving the carotid and middle cerebral artery vessels causing bilateral stroke and weakness. .He had a high risk of thrombotic events considering high platelet counts, advanced age and a positive genetic mutation. Accordingly, he was started on cytoreductive therapy with hydroxyurea along with antiplatelet medications. He was also continued on exercises and physiotherapy. He had improvement in speech and motor symptoms and remains stable on follow up.

CONCLUSION:

We aim to highlight two points in this report. Essential Thrombocythemia is one of the rare causes of stroke and the presence of a high platelet count should alert the clinician to this possibility. Genetic mutation analysis should be considered in all such cases as it would impact the treatment and the long term outcome. Early diagnosis and treatment leads to good long term outcomes.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal

ETHICAL APPROVAL

All necessary institutional ethical approval taken

REFERENCES

1. Cervantes F. Management of essential thrombocythemia. Hematology Am Soc Hematol Educ Program. 2011;2011:215-21.

2. Brière JB. Essential thrombocythemia. Orphanet J Rare Dis. 2007 Jan 8;2:3.

3. Tefferi A, Barbui T. Polycythemia Vera and Essential Thrombocythemia: 2019 update on diagnosis, risk-stratification and management. Am J Hematol. 2019;94(1):133-143

4. Rumi E, Pietra D, Ferretti V, Klampfl T, Harutyunyan AS, Milosevic JD et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014 Mar 6.123(10):1544-51

5. Rotunno G, Mannarelli C, Guglielmelli P, Pacilli A, Pancrazzi A, Pieri L et al.Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014 Mar 6;123(10):1552-5

6. Pietra D, Rumi E, Ferretti VV, Di Buduo CA, Milanesi C, Cavalloni C et al . Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms. Leukemia. 2016 Feb;30(2):431-8.

7. Michiels JJ, Berneman Z, Van Bockstaele D, van der Planken M, De Raeve H, Schroyens W. Clinical and laboratory features, pathobiology of platelet-mediated thrombosis and bleeding complications, and the molecular etiology of essential thrombocythemia and polycythemia vera: therapeutic implications. Semin Thromb Hemost. 2006 Apr;32(3):174-207

8.Harrison CN, Butt N, Campbell P, Conneally E, Drummond M, Green AR et al. Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia. Br J Haematol. 2014 Nov.167(3):421-3

9. Accurso V, Santoro M, Mancuso S, Napolitano M, Carlisi M, Mattana M et al .The Essential Thrombocythemia in 2020: What We Know and Where We Still Have to Dig Deep. Clin Med Insights Blood Disord. 2020 Dec 28;13

10. Barbui T, De Stefano V, et al. Addressing and proposing solutions for unmet clinical needs in the management of myeloproliferative neoplasm-associated thrombosis: A consensus-based position paper. Blood Cancer J. 2019;9:61.