Here we present a case of 55 year old male who presented with lower respiratory tract infection and clinical findings of systolic murmur at apex and hepatosplenomegaly and later on multiple cerebral emboli which on further evaluation turned out to be myeloproliferative neoplasm associated with cardiac mass with left ventricular mid-cavity obstruction.

Introduction
Myeloproliferative neoplasms (MPNs) may affect cardiovascular system presenting as valvular involvement, pericardial involvement, aortitis, arterial and venous thrombosis, pulmonary embolism, systemic and pulmonary hypertension etc. Hypertrophic cardiomyopathy as a manifestation of myeloproliferative neoplasms is a very rare finding. The signaling pathway of activated JAK-2 is linked to myocardial hypertrophy. However, only one case is reported till now with primary myelofibrosis with cardiac hypertrophy in which JAK-2 V617F mutation was demonstrated in hypertrophied cardiac myocytes on autopsy.2

Case Report
55 year old farmer presented with breathlessness of 1 week duration, intermittent fever and cough with scanty expectoration. He was treated for pulmonary tuberculosis 30 years ago and viral hepatitis 8 years ago.

On examination the vitals were normal. He had subconjunctival haemorrhage in left eye. Respiratory system examination showed features of left lower lobe consolidation. He had moderate hepatomegaly (4 cms below right costal margin) and moderate splenomegaly (about 13 cms below left costal margin) and was found to have mid-systolic murmur at the apex.

Investigations showed raised WBC count of 22,400/cmm with predominant neutrophils and normal eosinophils. The platelet count was normal. Chest X-ray showed obliteration of both costophrenic angles with nonhomogeneous opacity in left lower zone (Figure 1). ECG was normal.

2D-echo examination was done which showed mass lesion measuring about 3x2 cm attached to mid-lateral wall of left ventricle dividing the left ventricular cavity in two halves causing pressure gradient with resultant mitral regurgitation. No vegetations were visualized. Nature of lesion was suggestive of infiltrative disease of myocardium (Figure 2). He was treated as case of infective endocarditis with lower lobe consolidation with bilateral pleural effusion (with Inj. CP 20 lakh units IV 4 hrly, Inj. Gentamicin 80 mg IV 8 hrly).3 His blood culture did not show any growth of organism.

Peripheral smear report showed neutrophilia with a mild shift to left. USG abdomen showed mild hepatomegaly and moderate splenomegaly with bilateral minimal pleural effusion. With the treatment his condition improved and he became asymptomatic. However, as the splenomegaly was prominent strong possibility of a haematological malignancy was considered.
Patient was advised further evaluation for cardiac mass lesion and moderate splenomegaly but was not willing and was discharged against medical advice after 5 days of admission with advice to continue inj Crystalline Penicillin and inj Gentamycin. Antiplatelets (Aspirin 150 mg OD) and inj. Mannitol 100 ml iv 8 hrly (given 3 days) were started. Next day he had one episode of generalized seizures which was treated with inj. Lorazepam 4 mg iv stat and inj. Fosphenytoin 300 mg iv bolus followed by 150 mg iv 8hrly). He was also given unfractionated heparin 5000 units subcutaneously 8 hrly. Warfarin was added on 3rd day of starting heparin and heparin was stopped after 4 days of warfarin dosage. INR was kept around 2.5.

Cardiology re-evaluation corroborated previous Echo findings. His routine blood examination showed total WBC count of 38,900/cmm. Neutrophils were 98% and lymphocytes 2%. His serum LDH was also elevated to 1020 U/L (N: 114-240 U/L). Repeat peripheral smear showed tear drop RBCs and was indicative of myeloproliferative neoplasm (Figure 4).

With treatment patient showed improvement in sensorium but developed slowly progressive weakness on left side of the body. MRI brain and MR angiography was done after evaluation by neurologist which showed multiple foci of infarcts in bilateral cerebral and cerebellar hemispheres along with atrophic changes in brain (Figure 5). MRA showed normal
anatomy and morphology of circle of Willis and branches.

To determine the nature of cardiac mass lesion, cardiac MRI was done as biopsy was not possible. It showed the mass to be isointense with myocardium (Figure 6). Based on the peripheral blood smear report patient was started on Hydroxyurea 500 mg BD with close monitoring of blood counts.

At this time the power in both lower limbs and left upper limb had improved (grade 3/5) but right upper limb did not show significant improvement in the power (which was grade 1/5).

Hydroxyurea was stopped when his WBC count dropped to 10,000/cumm. Bone marrow aspiration biopsy was reported positive for JAK-2 mutation and negative for BCR-ABL fusion.

**Discussion**

PMF is characterized by marrow fibrosis, extramedullary haematopoiesis and splenomegaly. JAK-2 mutation is present in 50% of cases. Many patients are asymptomatic but others may have weight loss and other constitutional symptoms.

Our patient presented with clinical features suggestive of infective endocarditis and left lower lobe consolidation and later developed bilateral cerebral and cerebellar infarcts. His blood counts were persistently elevated with neutrophilic leukocytosis even after completing the course of antibiotics for infective endocarditis. From the beginning he had hepatomegaly with splenomegaly which is usual in case of infective endocarditis, though splenomegaly is rarely massive. Moreover echocardiography did not reveal any vegetation. As per the modified Duke’s criteria, the diagnosis of infective endocarditis must be made on the basis of echocardiography and / or blood culture. So from the beginning there was suspicion of primary haematological malignancy. After detailed evaluation the clinical picture was found to be fulfilling all 3 major (1. magakaryocyte proliferation and increased bone marrow cellularity, 2. not fulfilling PV, CML, MDS or other myeloid neoplasm criteria, 3. JAK2 V617F mutation) and at least 2 minor (raised LDH and palpable splenomegaly) WHO criteria for diagnosis of PMF.

The reason for bilateral ischemic stroke may be tumour emboli from the mass itself or emboli from an intracardiac thrombus which appears to be more likely in the setting of hypercoagulable state like MPN though Echo failed to show any intracardiac thrombus. Though provisional diagnosis was infective endocarditis anticoagulants were given with caution as the occurrence of the ischemic stroke was significantly late after starting the antibiotics and consideration was also given to the possibility of haematological malignancy.

Bone marrow aspirate evaluation showed features of JAK-2 mutation and confirmed the diagnosis of myeloproliferative disease. JAK STAT pathway has recently been shown to be an integral part of the response of the myocardium
to various cardiac insults, which includes hypertrophy and remodeling of myocardium.8

Six months after discharge the patient has developed exertional breathlessness due to regression of cardiac mass causing severe MR. The cardiac MRI which can reliably determine the nature of tissue suggests presence of myocardial tissue in mass lesion but the regression of myocardial hypertrophy still could not be explained. One possibility of myeloid sarcoma presenting as mass lesion was considered but could not be corroborated radiologically or haematologically.9

Myeloproliferative neoplasms especially PMF is characterized by constitutive mobilization of hematopoietic stem cells (HSC) and progenitor cells (HPC) into the peripheral blood. This trafficking leads to the establishment of extramedullary sites of hematopoiesis.10 Also these CD34+ cells have been shown to transdifferentiate into cardiac myocytes in vivo and in vitro.11 It may be proposed in this case that similar transdifferentiation of JAK2V617F mutated CD34 cells to cardiac myocytes may have resulted in cardiac mass, which could explain regression of the mass after institution of hydroxyurea therapy.

Patient awaits valve replacement surgery. The critical location of lesion neither did allow valve replacement surgery earlier nor the biopsy which could have been crucial for confirming exact nature of the lesion and also for cytogenetic studies from cells in the mass.

**Conclusion**

Primary myelofibrosis is a rare disease and may have different cardiovascular manifestations. This case presents an unusual and rather rare manifestation of myeloproliferative neoplasms. Further studies are required in this regard. Newer drugs may be developed as more information is obtained. Recently Ruxolitinib, a JAK-2 inhibitor has been much into the discussion. It has cleared phase 3 trials and is awaited in India.12

**Fig. 7: Echocardiogram 6 months later showing marked regression in cardiac mass size and severe MR**

**References**


