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Nephrology

AN UNUSUAL CAUSE OF HEART FAILURE: POLYCYTHAEMIA VERA WITH PAH

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ABSTRACT The incidence of PAH in CMPD is unknown. When present, PAH in CMPD may be attributed to thrombo-embolism, which is a known complication of CMPD. CMPD and unexplained PAH has been reported in few case reports or few studies with limited cases. Pathophysiology may be related to pulmonary capillary obstruction from increased cellular components, platelet activation and aggregation, micro thrombose formation and stasis. We present the case of a middle aged lady with no previous co-morbidity, who presented with polycythaemia and biventricular failure. Evaluation revealed PAH with no evidence of pulmonary thrombo-embolism. Haematocrit, Serum erythropoietin assay and bone marrow analysis suggested polycythaemia vera. Unexplained PAH in CMPD is discussed.

KEYWORDS : MeSH: CMPD, PAH, Polycythaemia Vera

Introduction:
Chronic myeloproliferative disorder (CMPD) may present with a variety of symptoms, usually to family physician or general physician. But CMPD presenting for the first time with heart failure is rare and a careful search did not reveal any such reported cases.

Case Report:
A 53 year old lady, postmenopausal, without adverse obstetric history and no history of addiction or high altitude residence, presented with one month history of progressive exertional dyspnoea and 15 days history of orthopnoea and bipedal edema. On the day of presentation she had acute breathlessness since morning. There was no history of angina, fever or cough. At emergency room, she was perspiring profusely with tachypnoea, tachycardia, SpO_2 64% at room air, plethoric look, cyanosis and bilateral fine basal crackles. ECG showed 'P' pulmonale with right axis deviation, T inversion in II, III, aVF and V1 – V6 and Chest radiograph showed bilateral perihilar homogenous opacity silhouetting the cardiac margin, suggestive of enlarged pulmonary trunks with paucity of lung vascular markings with raised right hemi-diaphragm (Figure 1). Trop T was negative.

Laboratory investigation showed Hb 21.9 gm/dl, TLC 5100/cmm, N 65 %, L 26 %, M 04 %, E 05 %, Platelets 70,000/cmm, Total RBCs- 6.6 x 10^{12}, PT- Test 20 sec/ Control 12 sec, aPTT- Test 40 sec/ Control 32 sec, INR 2.3, Total Bilirubin- 1.3 mg/dl, AST 25 IU/L, ALT 44 IU/L, ALP- 97 IU/L, BUN- 51 mg/dl, Serum Creatinine- 1.9 mg/dl, Na^+- 138 meq/L, K^+- 3.8 meq/L, Total protein- 6.1 gm, Albumin- 3.0 gm; HBs Ag, Anti HCV and HIV were negative. USG showed bilateral normal size kidneys with increased cortical echogenicity and normal movement of both hemi-diaphragms with respiration. 2D echocardiography showed no interatrial or interventricular septal defect, right atrium and ventricles were dilated with pulmonary arterial hypertension (PAH) (38 mm Hg + Right atrial pressure), there was no regional wall motion abnormality and LV ejection fraction was normal (PAH may have been underestimated by echocardiography because of presence of right ventricular dilatation and dysfunction). CECT thorax and pulmonary angiography showed grossly dilated pulmonary arteries (Main Pulmonary Artery- 4.0 cm, Right Pulmonary Artery- 2.4 cm, Left Pulmonary Artery- 2.6 cm) with pruning of its branches and no evidence of pulmonary thrombo-embolism (Figure 2).

Bone marrow biopsy showed hyper-cellular marrow for age with trilineage differentiation with no atypical cells or blasts. Serum erythropoietin was 3.2 mIU/ml (normal range 5.4 – 31 mIU/ml) and JAK2 mutation was not detected.

She was diagnosed as a case of Polycythaemia Vera (PV) with PAH with biventricular failure and was managed with 5 sessions of phlebotomy over one week period along with diuretics. Later Sildenafil and hydroxyurea was added. She responded well to treatment. Though at the time of discharge from hospital Hb was 18.5 gm, she maintained SpO_2 of 91-92% in ambient air and was ambulant. She did not require phlebotomy or hospital admission for heart failure during one year of follow up.

Discussion:
WHO has recently revised the classification of myeloid neoplasms and acute leukaemias in 2016. All these disorders share an origin in a multipotent hematopoietic progenitor cell; overproduction of one or more of the formed elements of the blood without significant dysplasia; and a predilection to extramedullary haematopoiesis, myelofibrosis and transformation at varying rates to acute leukaemia. As per the new classification system CMPD include chronic myeloid leukaemia (CML), chronic neutrophilic leukaemia and chronic eosinophilic leukaemia (which primarily express a myeloid phenotype) and polycythaemia vera, primary myelofibrosis (MF), and essential thrombocythaemia (ET) (in which erythroid or megakaryocytic hyperplasia predominates) [1]. This is not majorly different from the classification recommended in 2008, apart from mastocytosis now being given a separate category and not classified under myeloid neoplasms. WHO also defines the criteria for diagnosis of PV [1](Table 1). Our patient satisfied 2 major and 1 minor criteria.

PAH is defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg. WHO has classified aetiology of PAH into 5 categories. Category 1 includes idiopathic and familial causes, also PAH associated with connective tissue diseases, drugs and toxins, HIV, portal hypertension, schistosomiasis, etc. Category 2 includes PAH due to left heart disease, category 3 is PAH due to chronic obstructive pulmonary disease (COPD), category 4 is PAH due to chronic pulmonary arterial thrombo-embolism and category 5 includes PAH due to unclear or multifactorial aetiology, which includes CMPDs. Our patient falls in category 5 of PAH.

CMPD and PAH has been reported in few case reports or few studies with limited cases. The incidence of PAH in CMPD is unknown and when present, may be attributed to chronic thrombo-embolism which is a known complication of CMPD or other causes of PAH like left heart disease or COPD. Incidence of unexplained PAH in CMPD, which cannot be explained by mere association of both conditions, is infrequent. Case reports of PAH associated with thrombocytosis had been reported in the 90s [2-4]. In these cases PAH has been attributed to either overt or chronic and silent thrombosis in pulmonary vasculature; due to pulmonary capillary obstruction from increased cellular components, platelet activation and aggregation, micro thrombose formation and stasis.

Dingli D et al [5], in their retrospective series of 26 cases of CMPD with unexplained PAH, 92% had symptoms related to PAH and median time to diagnosis after CMPD was 8 years. They reported correlation of PAH with level of platelet count and haematocrit; also higher mortality contributed by PAH. V Garypidou et al [6], in their prospective series of

24 cases of CMPD without any symptoms attributable to PAH, found PAH by transthoracic echocardiography (TTE) in 40% patients. In their series, there was a preponderance of cases of ET with PAH. Haematological parameters were not predictive of presence of PAH. They did not report significant adverse events attributable to PAH, though the follow up period was short. R Gupta et al [7], in their prospective series of 25 cases of CMPD, found PAH in 48% by TTE. Though they had a preponderance of cases of PV, PAH was more prevalent among cases of ET. They did not report correlation between haematological parameters and PAH and their patients were asymptomatic at diagnosis and remained so during short follow up period.

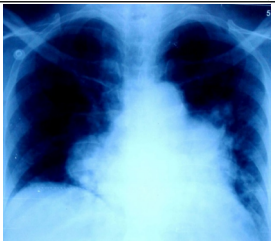
In our patient coagulation profile was abnormal with low platelet count and normal liver function test. There was no clinical or radiological evidence of chronic liver disease and viral markers were negative. Right hemi-diaphragm was raised with most of liver lying in thoracic cavity, but there was no enlargement of liver or spleen which normally happens if there is significant extra-medullary haematopoiesis and there was no evidence of portal hypertension. A state of chronic disseminated intravascular coagulation has been described with thrombocytosis in myeloproliferative states, contributing to microthromboses [8]. However, our patient had a low platelet count, which can only be explained by platelet utilisation in thrombosis, though CT pulmonary angiography did not reveal thromboembolism. Renal dysfunction was detected in our patient with estimated glomerular filtration rate (eGFR) by Cockcroft-Gault formula of 29.53 ml/min. Imaging showed normal sized but hyperechoic kidneys with no active sediment in urine or proteinuria. Kidney biopsy could not be done because of low platelet count and deranged coagulation profile. PV has been associated with glomerulopathies like focal segmental glomerulosclerosis and IgA nephropathy and abatement of proteinuria with therapy has been shown [9,10].

Conclusion:

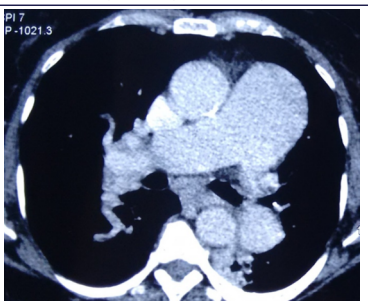
Unexplained PAH is common among cases of CMPD. Platelet count and haematocrit, may not correlate with presence or severity of PAH. Aetiology of PAH in these patients is multifactorial and may be related to stasis, micro-thrombo-emboli in pulmonary capillaries. Drugs (Tyrosine kinase inhibitors, Anagrelide) used for treatment of CMPD may also be causative. Symptomatic PAH portends a poor prognosis, though the extent and nature of disease remains unknown.

Since PAH appears to be common in patients with CMPD, more studies are needed to study the long-term impact of PAH on survival in these patients. Impact of therapy, including platelet-lowering agents and aspirin, on development and progression of PAH also needs to be studied.

Table 1. WHO PRV criteria
Major criteria:
1. Hemoglobin >16.5 g/dL in men Hemoglobin >16.0 g/dL in women or Hematocrit >49% in men Hematocrit >48% in women Or Increased red cell mass (RCM)
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criterion:
Subnormal serum erythropoietin level
(*Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion*)



(Figure 1: Chest radiograph showing hilar prominence and paucity of lung vascular marking)



(Figure 2: Axial CECT thorax image showing enlarged main pulmonary trunk, right and left pulmonary arteries with pruning of its branches)

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