SEVERE PAH WITH RENAL FAILURE

BKS Sastry

CASE DETAILS

A 32 Year Male patient by name K.KONDAIAH R/O Nalgonda was admitted on 18-07-2016 with complaints of Shortness of breath for one month, pedal edema for 2 days, decreased urine output for one day. He was apparently asymptomaic 1 month back and the illness started as SOB, insidious in onset, progressive to NYHA class I to III which has worsened during last 2 days to class IV associated with orthopnea and PND. It was associated with dry cough but no hemoptysis or fever. He developed bilateral pedal edema of pitting in nature during last 2 days and his urine output was decreased during the last 24 hours. No h/o fever, weight loss, rash or drug allergy. There was no h/o hypertension, diabetes, CAD, CKD or KOCH's or thyroid disorder. He was not habituated to smoking and not addicted to alcohol. Bowels and micturition was normal.

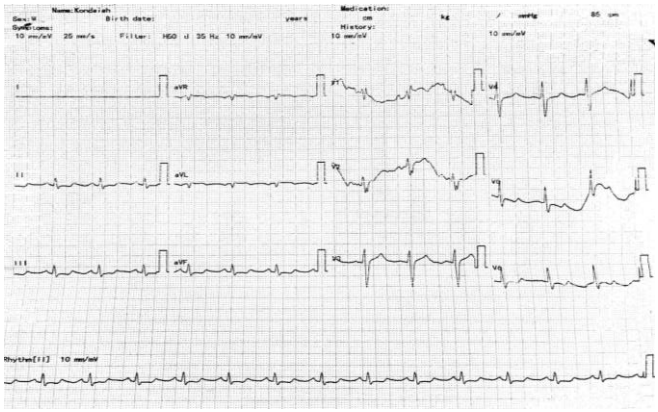
He was very sick during admission. Pulse rate was 96/min feeble and BP was 60 mm Hg systolic. General condition was poor with mild icterus and bilateral pitting pedal edema. No pallor, cyanosis, clubbing or lymphadeno - pathy. Systemic examination showed raised JVP, CVS- S1, S2 normal, R/S bilateral NVBS occasional rales, P/A soft with tender hepatomegaly, CNS – no focal deficit. ECG showed Sinus tachycardia, RBBB with secondary ST-T changes.

2D ECHO – RA/RV dilated with moderate RV dysfunction, Severe PAH with RVSP 72mm Hg (by TR jet velocity), Severe TR, no RV or LV hypertrophy with Good LV function, no MR , AR, Pericardial effusion, clot or vegetation. X ray chest AP view (bed side) showed mild cardiomegaly with prominent para-hilar area, no obvious pulmonary parenchymal pathology. Provisionally diagnosed as Acute pulmonary thromboembolism with right heart failure cardiogenic shock with Acute kidney injury was made.

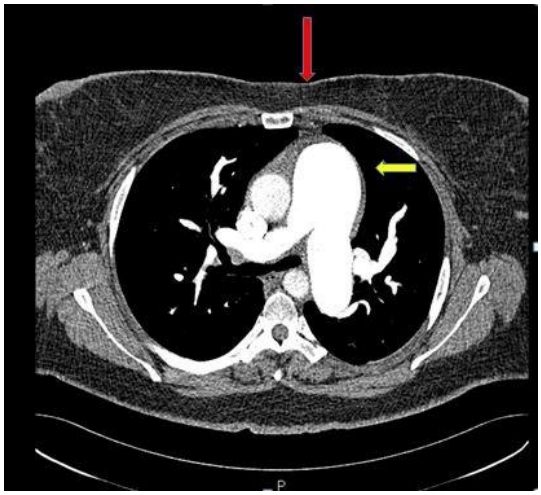
BKS Sastry,
Sr.Consultant, CARE Hospitals,Hyderabad
Corresponding Author: BKS Sastry
Email: bkssastry@hotmail.com

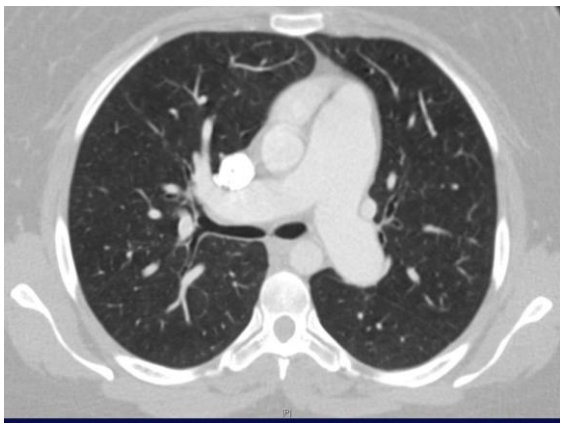
Preliminary investigations- CBP – Hb 11.8, TLC – 11800, DC – N-74,L-22, E- 2, M-2, B-0, PC-1.5 lakhs/dl, RBS – 223 mg/dl, Urea – 227mg/dl, S. Creatinine 6.0mg/dl, Sodium 120 mmol/l, Potassium 6.0 mmol/l, Chloride 72 mmol/l, SGOT 479 U/l, SGPT 350 U/l, ALP 53 U/l, Total serum bilirubin 2.6 mg/dl, direct bilirubin 1.9 mg/dl, Total protein 6.9 gr/dl, albumin 4.1 gr/dl, LDH 497 IU/l, CPK 231 IU/l, PT – 21.4 INR 1.9, APTT – 31.5. ABG at the time of admission showed PH -7.09, HCO3 6.7 mmol/l, PaO2 103, PaCO2 22.5, lactate 6 mmol/l suggestive of severe metabolic acidosis with respiratory acidosis. CUE – Ph 6.5, Albumin 3+, sugar- nil, Ketones – negative, pus cells 4-5, epithelial cells 6-8, RBCs-nil. Urine culture – no growth, Blood cultures – sterile, NT-pro BNP – 13000 NG/DL.

CT pulmonary angiogram was done after obtaining high risk consent for procedure in view of raised renal parameters, which showed dilated main pulmonary artery with no evidence of pulmonary thromboembolism.



Patient was intubated and mechanically ventilated, started on dual inotropic therapy with Noradrenaline and Dopamine. Empirical antibiotic Ceftriaxone was started. Anti hyperkalemia measures and Bicarbonate infusion were given. Nephrologist's consultation was taken and started on peritoneal dialysis. But the patient condition deteriorated despite of therapy and went into sustained hypotension cardiac arrest within 12 hrs of admission. His dead body was sent for autopsy to establish the cause of death.





DISCUSSANT : Dr. BK Sasty

This is the case of a young man who was asymptomatic till one month ago and then rapidly developed severe pulmonary artery hypertension with right heart failure and renal failure. Pulmonary hypertension is defined as pulmonary artery mean pressure more than 25 mm Hg with normal or reduced cardiac output 1. Though ideally right heart catheterization is needed to accurately diagnose pulmonary hypertension, in this patient with an estimated right ventricular systolic pressure of 72 mm Hg which is more than systemic pressure, right atrial and right ventricular and main pulmonary artery dilatation and absence of any gradient across pulmonary valve, a diagnosis of pulmonary hypertension can safely be made 2.

Though ECG is not very diagnostic in PAH, absence of dominant right ventricular forces would suggest that PH is not of long duration. History of one month duration symptoms would support that his pulmonary hypertension must have progressed rapidly in the last one month and it is probably not an acute decompensation of a chronic disease.

Pulmonary Hypertension has been classified in to five different groups based on etiology, patho physiology, natural history and response to treatment 3.

In this patient, echocardiographic does not show any left heart systolic and diastolic dysfunction, mitral valve disease, left ventricular inflow and outflow obstructive lesions and thus rules out Group II pulmonary hypertension.

Absence of any history to suggest long standing pulmonary disease, normal lung parenchyma on chest radiograph as well as CT scan of the chest and absence of respiratory acidosis rule out class III pulmonary hypertension.

Ventilation and perfusion scanning of the lungs is the method of choice to rule out pulmonary thrombo embolic disease 4. However a normal CT pulmonary angiogram in this kind of sick patient effectively rules out pulmonary vascular obstruction including thrombo embolic diseases either acute or chronic as the cause of his condition. Normal mediastinal imaging has also ruled out any mediastinal masses encasing pulmonary arteries thus causing severe pulmonary hypertension. CT pulmonary angiogram ruled out Group IV pulmonary hypertension in this patient.

Pulmonary hypertension due to Group V is a miscellaneous group and patient does not have any clinical features to suggest any of them.

Pulmonary hypertension of group 1 has different etiologies. Idiopathic pulmonary artery hypertension is a diagnosis of exclusion. He has no family history of PAH. IPAH and FPAH cannot be differentiated from each other but neither of them would generally present with such a stormy course and associated renal failure is unexplained and absence of right ventricular hypertrophy on ECG or echo is unexpected. Patient does not have obvious shunt lesion on echocardiogram and his oxygen saturation at admission is normal ruling out any PAH due to congenital heart disease with shunt lesions. He has no history of chronic liver disease. Ultra sound scan of abdomen would have helped us to rule out any chronic liver disease or portal hypertension 5. However, his biochemical liver function tests do not suggest any chronic liver disease. Serum albumin value

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Pulmonary hypertension of group 1 has different etiologies. Idiopathic pulmonary artery hypertension is a diagnosis of exclusion. He has no family history of PAH. IPAH and FPAH cannot be differentiated from each other but neither of them would generally present with such a stormy course and associated renal failure is unexplained and absence of right ventricular hypertrophy on ECG or echo is unexpected. Patient does not have obvious shunt lesion on echocardiogram and his oxygen saturation at admission is normal ruling out any PAH due to congenital heart disease with shunt lesions. He has no history of chronic liver disease. Ultra sound scan of abdomen would have helped us to rule out any chronic liver disease or portal hypertension 5. However, his biochemical liver function tests do not suggest any chronic liver disease. Serum albumin value more than 4.1 grams/dl rules out chronic liver disease. Patients with severe right heart failure like this patient can have mild elevation of serum bilirubin and also elevation of SGOT and SGPT. Higher SGOT value than SGPT generally suggests liver disease secondary to cardiac disease. Patient has short duration history and apparently no history of intake of drugs causing PAH. Further, apart from history, it is difficult to differentiate it from IPAH. Patient is not a known carrier of HIV infection and generally it does not present so acutely. Patient has no clinical features to suggest any connective tissue disease. However serological tests like ANA profile to rule out any connective tissue disease would have been helpful but the same is not available in this patient. This is particularly pertinent in this patient who has renal failure.

Patient has history of orthopnea and PNDs in the final two days of his life. These can occur in patients with pulmonary veno occlusive disease. However, these patients have typical findings like Kerley B lines or intersegmental septal thickenings, mediastinal lymphadenopathy and pleural effusions, none of which

are present in this patient 6. Orthopnea and PND might have been due to fluid overload state due to renal failure that this patient had terminally. Similarly pulmonary capillary hemagiomatosis would also have typical CT imaging features which are missing in this patient.

Patient has features of renal failure. He has uremia, high anion gap metabolic acidosis, 3+ albuminuria. Shock due to any cause can produce acute renal failure. Such high values of urea and creatinine in short time and high anion gap acidosis without any obvious catabolic state make acute glonerulo nephritis as the likely cause of acute renal failure. Though chronic renal failure can occasionally cause pulmonary hypertension, this patient does not have features of chronic renal failure. Hemoglobin value of 11.8 in this male patient is low but not to the low levels generally seen in patients with chronic renal failure. He does not have chronic illness and absence of hypertension does not support a diagnosis of chronic renal failure. Bilateral small sized kidneys on ultrasound scan of abdomen and any renal dystrophy would have been more helpful to consider a diagnosis of chronic renal failure. Urine sediment is bland without any RBCs or casts does not fit with any rapidly progressive glomerulo nephritis.

Connective tissues diseases like scleroderma, systemic lupus erythematosus, mixed connective tissue diseases etc. are associated with both renal failure and pulmonary hypertension 7. But these are often seen female patients and other clinical features are more prominent and generally the presenting features. Pulmonary hypertension and renal failure though present in these patients seldom have such a rapid progression. Anti phopsholipid anti body syndrome either primary or associated with SLE can present as pulmonary thrombo embolism. However, the same has been ruled out in this patient.

By definition, diseases with pulmonary artery mean pressure more than 25 mm Hg and high cardiac output are not included considered as pulmonary hypertension and are not included in the classification. These disorders include thyrotoxicosis and beriberi. Patient does not have any clinical features of thyrotoxicosis.

Beriberi a disease due to thiamine deficiency often presents with pulmonary hypertension, right heart failure and high cardiac output. This is often seen in people who consume imbalanced diets with high carbohydrates and alcoholics 8,9. In early stages, patient will have clinical signs of high cardiac output like warm and dry extremities, bounding pulse, ejection systolic murmurs. Unrecognized and untreated beriberi can progress to cardio vascular collapse and shock like situation lading to rapid death 10. With cardio vascular collapse as the renal failure and metabolic acidosis appear, the signs of high cardiac output disappear. This terminally sick patient with supra systemic pulmonary hypertension, heart failure and cardiogenic shock is too sick to have clinical signs of high cardiac output. Considering the rapid progression of disease to cardiovascular collapse due to severe right heart failure, severe metabolic acidosis, acute renal failure, Shoshin type of beriberi has to be considered. This is especially so when all other causes of pulmonary hypertension are unlikely.

Beriberi is a disease due to thiamine deficiency. Thiamine is a coenzyme of pyruvate dehydrogenase an important enzyme in glucose metabolism. Thiamine deficiency may present as wet beriberi with pulmonary hypertension with right heart failure, dry beriberi with neuropathy or shoshin type that has cardiovascular collapse 11. Alcoholism, consumption of imbalanced highly polished rice, betel nut certain types of fish are risk factors for beriberi 12,13. Excess diuretic therapy with loss of water soluble vitamins may also precipitate beriberi.

Manifestations of Shoshin beriberi in the form of shock, severe metabolic acidosis, and multi organ failure can be misleading and challenging 14,15. Sometimes patients are non-alcoholics and may not have signs of overt malnutrition and the diagnosis may not even be considered. Beriberi is a clinical diagnosis and a high index of suspicion is needed. A therapeutic trial of thiamine infusion can be lifesaving in patient who present with cardiovascular collapse due to acute pulmonary hypertension and right heart failure and metabolic acidosis.

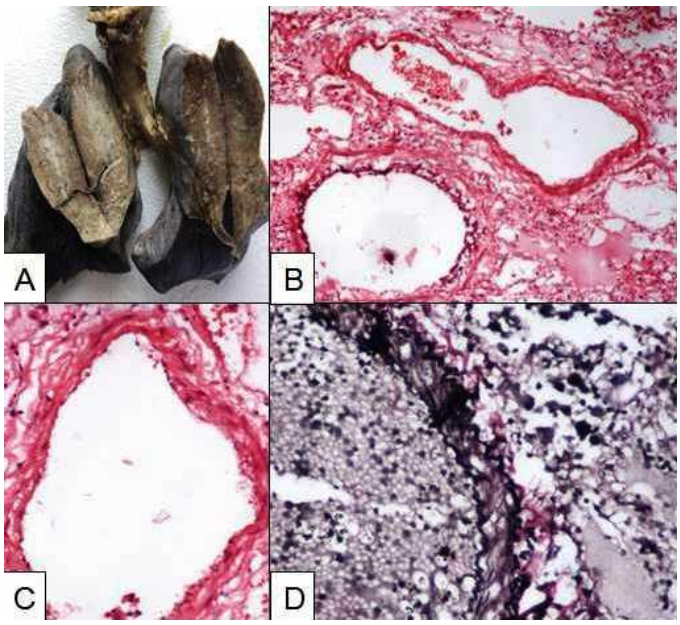
Final Diagnosis by discussant : Shoshin type Beriberi.

AUTOPSY FINDINGS :

A complete body autopsy was performed after taking informed consent within 3 hours after death. The organs were removed en bloc maintaining the anatomical

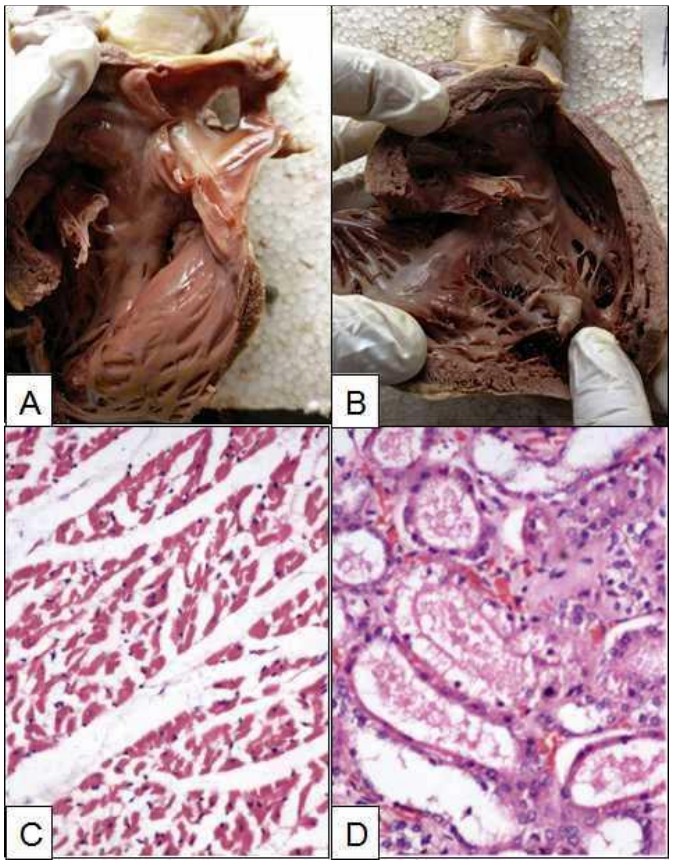
continuity after giving appropriate incisions. The right and the left lung weighed 550 gm and 500 gm respectively. Cut sections of both the lungs were subcrepitant. There was no evidence of any thrombi in the vessels. (Figure 1A). The pulmonary vascular bed was examined carefully on routine haematoxylin and eosin stain aided by elastic tissue stains. In normal lung the diameter of pulmonary artery is almost the same as its accompanying airway. The preacinar muscular pulmonary arteries usually have a medial thickness of 1-2% of the vessel diameter. Similar finding was noted in the present case. There was no thickening of the vessel wall or narrowing of the lumina. The elastic stains did not show any obvious increase in muscle layer with widening of the space between internal and external elastic lamina. There was no intimal proliferation, concentric laminar intimal fibrosis, fibrinoid necrosis or plexiform lesions. There was no muscularization of arterioles in lung parenchyma (Figure 1B-D).

Figure 1. A. Gross photograph of lung. B.Muscular pulmonary artery with accompanying bronchiole. The diameter of the vessel is similar to the diameter of bronchiole (Hematoxylin and eosin, x 100) C. Pulmonary artery donot show any muscular hypertrophy of the vessel wall. (Hematoxylin and eosin, x 400) D. The internal and external elastic lamina is highlighted on elastic stain. (Veroff Van Gieson x 400)



The heart weighed 300 gms. The right and left ventricular wall thickness measures 0.4 cm and 1 cm. There was no evidence of any right ventricular hypertrophy.(Figure 2A,B and C). The liver showed changes of chronic venous congestion and the spleen was enlarged with congestive splenomegaly. The bilateral kidneys showed changes of acute tubular necrosis with vacuolization and desquamation of the tubular epithelial cells.(Figure 2 D) The gross and microscopic examination of the rest of the organs were unremarkable.

Figure 2. A and B. Gross photograph of the heart showing right ventricle with semilunar valves and part of the pulmonary trunk. C. There is no disarray or enlargement of the cardiac myocytes (Hematoxylin and eosin x 400) D.Vacuolization and desquamation of the tubular epithelial cells.(Hematoxylin and eosin x400)



Final autopsy finding are normal heart and lung with acute tubular necrosis of Kidney.

Probable Dignosis : BERIBERI with severe irreversible cardiogenic shock with ATN .

Limitation of this CPC : Patient recived thiamine injection during hospital stay, but without any improvement of the shock state. This may that patient reached hospital quite late in irrevesrsible stage of shock. As autopsy is demonstrating any other diseases probably BERIBERI is the final diagnosis.

For practical reasons, replacing thiamine as an initial test may be most feasible. If the patient responds to treatment, it is safe to assume that a measure of thiamine deficiency was responsible for the condition. Thiamine is not toxic in high levels, which means that this route carries little risk. In addition, time is saved in treating the patient and money is saved in testing. (However, although observation of a patient's clinical response to thiamine administration remains the easiest, least expensive form of testing, clinicians usually miss the subclinical forms of beriberi.

If laboratory confirmation is needed, measure blood thiamine, pyruvate, alpha-ketoglutarate, lactate, and glyoxylate levels. Also, measure urinary excretion of thiamine and its metabolites. The scarcity of any of these chemicals strongly suggests thiamine deficiency.

In conjunction with whole blood or erythrocyte transketolase activity preloading and post loading, a thiamine loading test is the best indicator of thiamine deficiency. An increase of more than 15% in enzyme activity is a definitive marker of deficiency. However, this test is expensive and time consuming; it is performed only for criterion-standard proof of deficiency.

Measure urinary methylglyoxal; also measure serum thyroid-stimulating hormone (TSH), to rule out thyrotoxicosis-induced high-output heart failure, if applicable.

An increase in troponin I has been found in heart failure due to thiamine deficiency. Thiamine is an important enzymatic cofactor in several energy pathways. Its deficiency disrupts cellular processes and leads to myocardial death. Thiamine is also an important factor in the cellular production of glutathione, an antioxidant that myocardial cells need to counteract free radicals. In the absence of glutathione, these cells would die prematurely.

Metabolic acidosis can be seen in thiamine deficiency. This is due to increased lactic acid production from thiamine deficiency. Thiamine pyrophosphate (thiamine derivative) is the coenzyme for the conversion of pyruvate to acetyl coenzyme A. Without it, pyruvate is under used and converts to lactate. It is important to consider thiamine deficiency in the presence of unexplained metabolic acidosis, specifically, lactic acidosis.

References:

1. Barst RJ, McGoon MD, Torbicki A, Sitbon O, Krowka M, Olschewski H, Gaine SP. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004; 43: 40S–47S

2. Rudski LG, Lai WW, et al.. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.

3. Galiè N, Humbert M, Vachiery JL et al . 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119.

4. Tunariu N, Gibbs SJR, Win Z, et al. Ventilation-perfusion scintigraphy Is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680–684.

5. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: results from a 10-year screening algorithm.

Hepatology 2006; 44:1502–1510.

6. Resten A, Maitre S, Humbert M, Rabiller A, Sitbon O, Capron F, Simonneau G, Musset D. Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. Am J Roentgenol 2004;183:65–70.

7. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522–3530.

8. Watson JT1, El Bushra H, et al. Outbreak of beriberi among African Union troops in Mogadishu, Somalia. PLoS One. 2011;6:e28345.

9. Chen KT1, Chiou ST, et al. Cardiac beriberi among illegal mainland Chinese immigrants. J Int Med Res. 2001;29:37-40.

10. Campbell CH. The severe lactic acidosis of thiamine deficiency: Acute pernicious or fulminating beriberi. Lancet 2: 446–9.

11. McIntyre N, Stanley NN. Cardiac beriberi: two modes of presentation. Br Med J. 1971;3:567–569.

12. Thiamine deficiency and its prevention and control in major emergencies. World Health Organization. Geneva, 1999.

13. Bhuvaneswaran C, Sreenivasan A. Problems of thiamine deficiency states and their amelioration. Ann N Y Acad Sci 98: 576–601.

14. Rama Prakasha Saya, Shashidhar et al. Clinical Correlates and Outcome of Shoshin Beriberi. N Am J Med Sci. 2012; 4: 503–506.

15. Engbers JG, Molhoek GP, Arntzenius AC (1984) Shoshin beriberi: a rare diagnostic problem. Br Heart J 51: 581–2.