PULMONARY VENO OCCLUSIVE DISEASE- A RARE CAUSE OF PULMONARY ARTERIAL HYPERTENSION

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Abstract:
Pulmonary veno occlusive disease (PVOD) is a rare cause of pulmonary arterial hypertension (PAH). The pathologic hallmark of PVOD is extensive and diffuse occlusion of the pulmonary veins by fibrous tissue. Most patients have nonspecific complaints and the clinical signs closely resemble idiopathic PAH. There are no definitive clinical criteria for the diagnosis of PAH and surgical lung biopsy is the current gold standard for diagnosis. Therapeutic options include long term oxygen therapy, oral anticoagulation with a target INR of 2 to 3, vasodilators and immunosuppressive therapy in case of association with autoimmune disease. The efficacy of current therapeutic options in not established owing to the rare nature of the disease and lack of randomized control trials. The prognosis of PVOD is poor and most patients die within two years of diagnosis. Keyword: Pulmonary veno occlusive disease (PVOD), Pulmonary arterial hypertension (PAH)

A 29 year old female presented with a two month history of progressively worsening breathlessness on exertion. Her effort tolerance on level ground was 300m. This was associated with facial puffiness and swelling of both lower limbs. There was no history of chest pain or palpitations on exertion. There was no past history suggestive of rheumatic fever. There was no history suggestive of connective tissue disease. On examination, her pulse rate was 92 beats per minute, regular with normal volume and character, blood pressure in the right upper limb was 100/80mmHg and her respiratory rate was 28/min. Her oxygen saturation was 92% on room air. Her jugular venous pressure was elevated at admission. On auscultation, the pulmonary component of the second heart sound was loud. The remainder of her cardiac and respiratory auscultation was within normal limits. The rest of the general and systemic examination was within normal limits. Investigations revealed normal blood picture with normal renal and liver function tests. A connective tissue workup revealed ANA positivity. Urinalysis was negative for proteinuria. Her electrocardiogram showed
sinus rhythm with features of right ventricular hypertrophy.

Chest Xray(Figure 1) showed cardiomegaly with a prominent pulmonary artery shadow and spirometry showed a restrictive pattern. Echocardiogram revealed grossly dilated right atrium and ventricle with an intact interatrial septum with severe tricuspid regurgitation(TR) and severe pulmonary arterial hypertension (PAH). She underwent a CT pulmonary angiogram with HRCT thorax which showed a dilated main pulmonary artery (MPA); dilated RA and RV and enlarged SVC, IVC and hepatic veins -in keeping with pulmonary arterial hypertension; and diffuse areas of ground glass opacification in bilateral lung fields (Figure 2) with few patchy areas of low attenuation. There was also minimal intralobular interstitial thickening with few ground glass centri-lobular nodular opacities. The overall picture of her findings of HRCT thorax was consistent with pulmonary veno-occlusive disease. We initiated our patient on Warfarin, Nifedipine and immunosuppression with Prednisolone and Azathioprine. After six months of follow up, she had symptomatic improvement of her breathlessness and a minimal increase in her effort tolerance.

DISCUSSION:
Pulmonary arterial hypertension (PAH) still remains a cause of significant morbidity and mortality. Pulmonary veno occlusive disease (PVOD) is a rare and underdiagnosed cause of PAH. PVOD, as the name suggests, is a clinico-pathological entity characterized by occlusion or narrowing of the pulmonary veins and venules by sometimes loose, sometimes more dense and collagen-rich, fibrous tissue, leading to clinical manifestations of PAH[1]. Although the term PVOD was first used in the 1960s, the first case was described by Dr J. Hora in 1934 in a 48-year-old patient who died within 1 year of diagnosis with symptoms of right-sided heart failure[2]. The terms "isolated pulmonary venous sclerosis," "obstructive disease of the pulmonary veins," and "venous form of primary pulmonary hypertension" were previously used to describe the syndrome.

The pathologic hallmark of PVOD is extensive and diffuse occlusion of the pulmonary veins by fibrous tissue; which may be loose and edematous, or dense. and sclerotic. The exact pathophysiology of PVOD still in unclear. Multiple theories have been postulated with regards to the above and these include genetic[3], infections - recent infection with Toxoplasma gondii or measles, Epstein-Barr Virus or Cytomegalovirus infection[4,5], toxins - chemotherapeutic agents like bleomycin, mitomycin and Carmustine[6], underlying prothrombotic state[7,8] or autoimmune - in association with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis [9]. Most patients present late with nonspecific complaints likedyspnea on exertion, lethargy and chronic cough [10].Clinical examination usually reveals features of right heart failure and a loud pulmonary component of the second heartsound, right-sided cardiac murmurs (eg, tricuspid regurgitation). Crepitations may occur in patients who have prominent chronic pulmonary infiltrates and decreased breath sounds with dullness to percussion may exist inpatients with pleural effusions. Chest radiograph may show engorgement of the central pulmonary arteries and scattered patchy parenchymal opacities and Kerley B lines. CT scan usually reveals smooth septal thickening, diffuse or mosaic ground glass opacities, multiple small nodules, pleural effusions, or areas of alveolar consolidation[11].
These ground glass opacities may result from alveolar septal thickening with associated hyperplasia of lining epithelium. Prominent mediastinal lymphadenopathy has been noted in some cases, as a consequence of venolymphatic shunts and circulating angiogenic factors. Pulmonary function testing may reveal reduced single-breath diffusing capacity for carbon monoxide (DLCO) and a restrictive ventilatory defect.

There are no well-defined criteria for the diagnosis of PVOD as this cannot be distinguished from idiopathic PAH on the basis of history and physical findings. A triad of severe PAH, radiographic evidence of pulmonary edema and normal pulmonary artery occlusion pressure is suggestive of PVOD [12]. A definitive diagnosis of PVOD can be made on a surgical lung biopsy; which may show sclerosed venules with intimal sclerosis and occasionally hemosiderosis. Thence, to make a definitive diagnosis via surgical lung biopsy is questionable. Though vasodilators have a significant role in the treatment of idiopathic PAH, their efficacy in PVOD is unclear. Though there are few case reports which state that Nifedipine, Hydralazine, and Prazosin may be used [13,14]. This data is from very small numbers and requires consolidation in the form of future trials. Immunosuppressive agents like high-dose steroids and Azathioprine have been used in PVOD, especially when associated with an autoimmune disease [15,16]. Owing to the paucity of data regarding the efficacy of the above modalities and since patients with PVOD have limited therapeutic options, a trial of vasodilators and immunosuppression in recommended under close monitoring. Also, since observational studies have demonstrated the efficacy on oral anticoagulation in PAH [17] and since the basic pathology in PVOD is thrombotic occlusion of the pulmonary veins, oral anticoagulation with a target International Normalized Ratio (INR) of 2 to 3 is recommended. Long-term oxygen therapy has been recommended for hypoxemic patients with PVOD [18]. Thence, case reports have described lung transplantation as the only therapy which significantly prolongs life expectancy [19,20,21]. The cumulative evidence for this is lacking. Experimental therapies for PVOD include Defibrotide, which being an adenosine receptor agonist leads to increased concentrations of endogenous prostaglandins (PGI2 and E2) thus leading to veno-dilation [22]. Imatinib is a tyrosine kinase inhibitor which also inhibits platelet derived growth factor, thus helping invascular remodelling [23]. If left untreated, PVOD may cause death within two years of diagnosis in most patients [24].

In conclusion, since PVOD is a rare disease, randomized control trials testing the efficacy of various treatment modalities is impossible and the current basis for treatment is only based on case reports and case series.

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