Pulmonary Veno-occlusive Disease

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As a rare form of pulmonary hypertension, the pathophysiology and clinical presentation of pulmonary veno-occlusive disease (PVOD) has long remained poorly understood. In this review, we will discuss the distinctions between presentation of PVOD and pulmonary arterial hypertension, and address the importance of early diagnosis in proposing specific management. We will explore the risk factors and conditions associated with PVOD, and describe the challenges surrounding its diagnosis and management.

Even though the first description of pulmonary veno-occlusive disease (PVOD) was reported in 1934, the pathophysiology and clinical presentation of this orphan disease has long remained poorly understood.[1,2] While the pulmonary vascular pathology of idiopathic or heritable pulmonary arterial hypertension (PAH) is characterized by major remodeling of small precapillary pulmonary arteries, PVOD mainly affects the postcapillary pulmonary vessels, including the small pulmonary veins and capillaries.[3-5] PVOD often has a very similar clinical presentation to PAH, but is characterized by a risk of developing severe pulmonary edema with PAH-specific therapies and a worse prognosis, justifying the importance of an early diagnosis to propose specific management. Recently, a better characterization of the disease has allowed identification of risk factors, including biallelic mutations of the *EIF2AK4* (eukaryotic translation initiation factor 2 alpha kinase 4) gene,[6] connective tissue diseases, and exposure to organic solvents or alkylating agents. Although a definitive diagnosis of PVOD requires histological analysis,[7,8] surgical lung biopsy represents a very high-risk procedure in these patients and is not recommended[9]; therefore, a noninvasive approach should be used to evaluate patients.[10]

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CLASSIFICATION

The current classification from the 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) Guidelines on the Diagnosis and Man-

agement of Pulmonary Hypertension (PH) divides PH into 5 main groups according to shared pathophysiology, clinical features, and therapeutic approaches (Table 1).[9] Based on recent advances in clinical description and genetics, PVOD and pulmonary capillary hemangiomatosis (PCH) are now considered a common entity and represent varied expressions of the same disease.[9] Additionally, occlusive venopathy and capillary proliferation may occur in PAH associated with different conditions, recently demonstrated as frequently the case in PAH associated with connective tissue diseases.[11,12]

PATHOLOGIC ASSESMENT

PVOD is characterized by postcapillary lesions involving septal veins and preseptal venules, with muscularization of the tunica media and loose, fibrous remodeling of the intima, which may lead to total occlusion of the lumen (Figure 1). Fibrous occlusion of large septal veins is seen in many forms of secondary pulmonary venous hypertension,[1,13] thus involvement of preseptal venules should be considered as necessary for the diagnosis of PVOD. Pleural and pulmonary lymphatic vessels are usually dilated and signs of occult alveolar hemorrhage may be present.[14] Even if vascular lesions predominate within the septal and preseptal veins, lesions frequently affect capillaries and small pulmonary arteries.[3,5] In PVOD, pulmonary arterial lesions mainly consist of intimal thickening and medial hypertrophy, but plexiform lesions are absent. Capillary changes include dilated congested capillaries and focal capillary angioproliferations, and it has been proposed that this proliferation may follow chronic postcapillary obstruction.[3,4] Thrombotic occlusion of small postcapillary microvessels may be present, corresponding to "colander-like" lesions.

RISK FACTORS AND ASSOCIATED CONDITIONS IN PVOD

Epidemiology

A very wide range for age at diagnosis of PVOD has been reported, from the first weeks of life to an advanced age.[2,7,8] In

Table 1: Classification of PH According to ERS/ESC Guidelines[9]

I. Pulmonary arterial hypertension
I.I Idiopathic
I.2 Heritable
I.2.I BMPR2 mutation
I.2.2 Other mutations
I.3 Drugs and toxins induced
I.4 Associated with:
I.4.I Connective tissue disease
I.4.2 Human immunodeficiency virus (HIV) infection
I.4.3 Portal hypertension
I.4.4 Congenital heart diseases (Table 5)
I.4.5 Schistosomiasis
I′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
I′.I Idiopathic
I′.2 Heritable
I′.2.I EIF2AK4 mutation
I′.2.2 Other mutations
I′.3 Drugs, toxins and radiation induced
I′.4 Associated with:
I′.4.I Connective tissue disease
I′.4.2 HIV infection
I″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.I 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.I 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)[a]
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.I Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.I 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.I Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
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

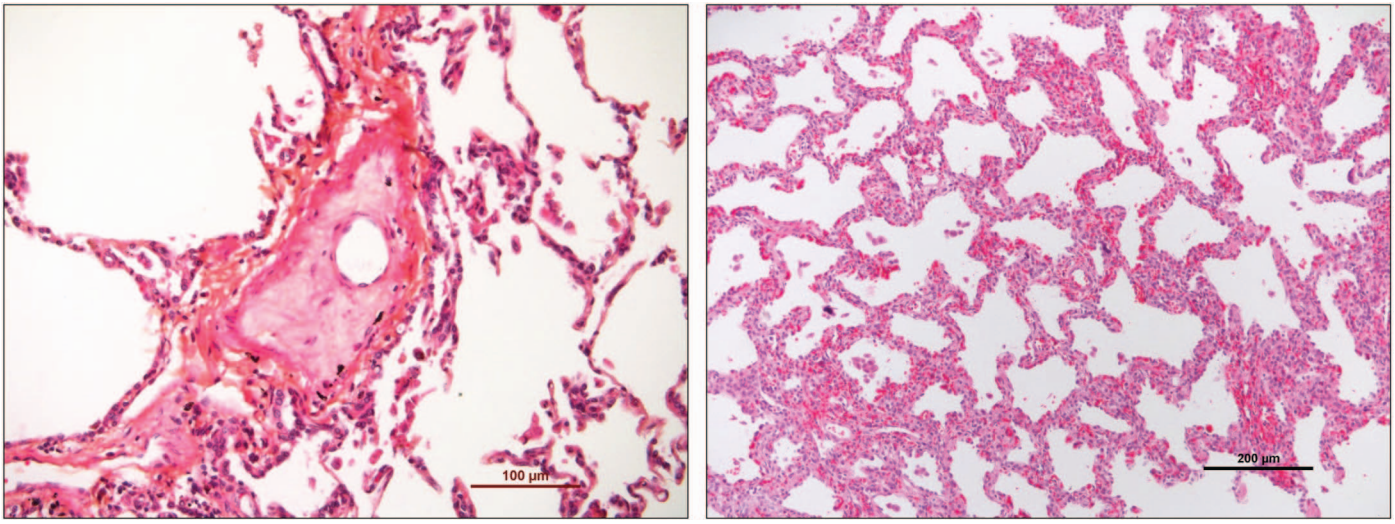

Figure 1: Pulmonary vascular lesions in a patient suffering from PVOD. A. Fibrous obstruction of a preseptal venule. B. Capillary lesions characterized by exuberant proliferation of endothelial cells.

contrast with idiopathic PAH, PVOD is not associated with a female predominance.[2,7] The incidence of PVOD is clearly underestimated, as many cases are classified as idiopathic PAH. PVOD is presumed to account for 5% to 10% of histological forms of cases initially thought to be idiopathic PAH; however, PVOD can also occur in other conditions (particularly systemic sclerosis) or may be associated with certain exposures (chemotherapy, solvent exposure).

Heritable PVOD

Genetic risk in the development of PVOD has been suggested previously by reports of occurrence in siblings.[15,16] In 2014, the French PH network reported the genealogy of 13 PVOD families with heritable PVOD.[6,17] Whole-exome sequencing on 2 affected siblings from 5 families allowed the demonstration that biallelic mutations in the *EIF2AK4* gene were present in all 13 PVOD families. Interestingly, one of the families carrying *EIF2AK4* mutations was initially diagnosed with PCH.[6] Subsequently, Best et al also identified *EIF2AK4* mutations in another PCH family and in sporadic PCH cases.[18]

Chemotherapy

A definite association between PAH and appetite suppressants (aminorex, fenfluramine and derivatives, benfluorex) has been clearly demonstrated based on epidemiological studies. We recently performed a systematic analysis of possible cases of chemotherapy-induced PVOD from the French PH network, and concluded that alkylating agents represent the predominant drug class associated with increased risk.[19] Indeed, we demonstrated that cyclophosphamide and mitomycin may induce venous lesions mimicking PVOD in different animal models.[19]

Organic Solvent and Tobacco Exposure

In a recent case-control study, we found that PVOD was linked to occupational exposure of organic solvents, particularly trichloroethylene.[20] PVOD patients with solvent exposure were characterized by older age of disease onset and the absence of mutations in the *EIF2AK4* gene.

We also found a higher tobacco exposure and an increased proportion of smokers in different series of PVOD patients as compared to idiopathic or heritable PAH patients.[2,20] Nevertheless, the reason why tobacco exposure would be a specific risk factor for PVOD remains unknown.

Connective Tissue Diseases

Venular involvement is common in connective tissue disease-associated PAH, particularly systemic sclerosis.[11,12] PVOD has also been reported to be associated with other inflammatory disorders such as sarcoidosis, Langerhans' cell granulomatosis, and Hashimoto's thyroiditis. We recently reported that as many as two-thirds of patients with precapillary PH due to systemic sclerosis may display radiological signs of PVOD on high-resolution computed tomography (HRCT) of the chest.[21]

DIAGNOSIS OF PVOD

Clinical Features

Clinical examination is often unhelpful in distinguishing PVOD and idiopathic PAH. As observed in other forms of PAH, affected individuals most frequently report dyspnea, exercise limitation, fatigue, and syncope. Hemoptysis may also occur but is rarely massive. Lung auscultation is usually normal, but auscultatory crackles may occur in the context of pulmonary edema. Digital clubbing and Raynaud's phenomenon have been reported in PVOD, but recent series suggested that these findings remain rare in PVOD and can also be found in the same proportion in idiopathic PAH.[2]

Hemodynamic Characteristics

In a large series comparing patients with biopsy-proven idiopathic PAH and PVOD, we found that PAH and PVOD share broadly similar hemodynamic characteristics, and we confirmed that PVOD patients were characterized by severe precapillary PH on right heart catheterization.[2] Even if PVOD is histologically characterized by postcapillary obstruction (involvement of small pul-

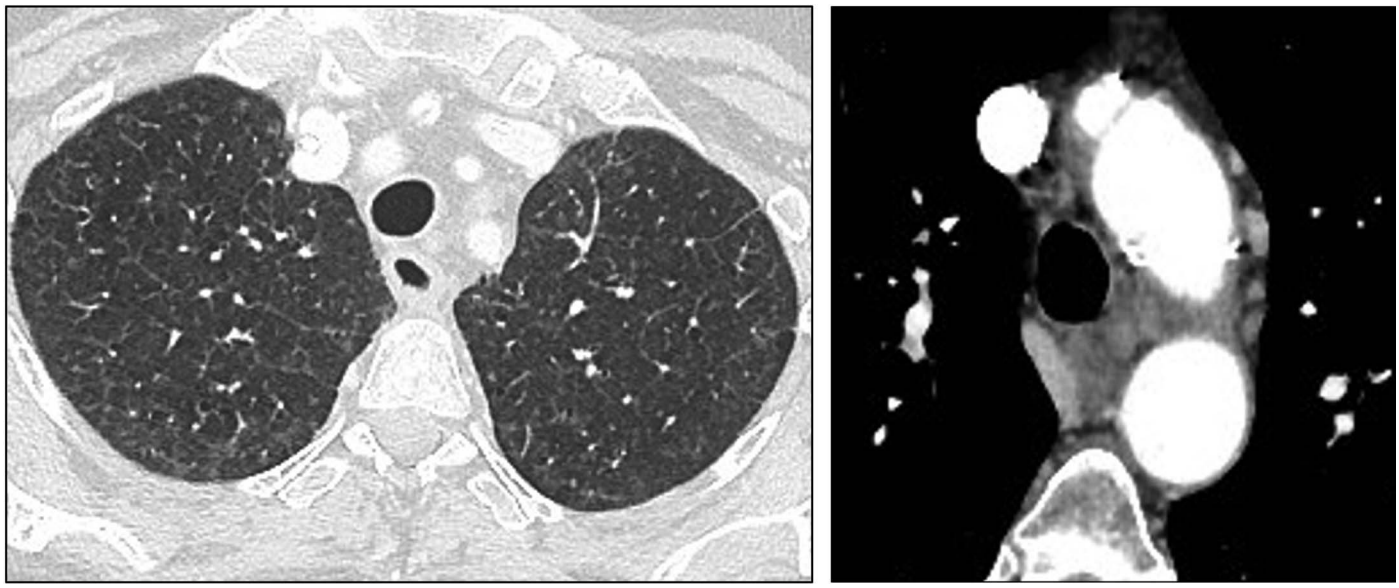

Figure 2: HRCT of the Chest in PVOD. A. HRCT of the chest showing septal lines and centrilobular ground-glass opacities. B. HRCT of the chest showing latero-aortic lymphadenopathy.

monary veins), pulmonary artery wedge pressure (PAWP) is normal in PVOD patients (<15 mm Hg). When PAWP is obtained during balloon occlusion, measurements that are recorded when a catheter is wedged in a branch of the pulmonary artery reflect pressures in the larger veins that extend distally toward the heart, and these vessels are typically unaffected by the disease process.[10] In PVOD, therefore, the apparently normal values of PAWP do not represent a reflection of the true capillary pressure. Of note, an acute vasodilator response has been reported in some PVOD cases.[2,22] However, an acute vasodilator response in PVOD was not predictive of a long-term response to calcium channel blockers.

Imaging Studies

Chest radiographs usually offer limited help in the differential diagnosis of PVOD unless pulmonary edema occurs after initiation of PAH-specific therapy. HRCT may be more helpful, showing a significantly higher frequency of centrilobular ground-glass opacities, septal lines, and mediastinal lymph node enlargement in PVOD compared with idiopathic PAH (Figure 2).[2,7,23,24] We have demonstrated that the presence of 2 or 3 of these radiological abnormalities is observed in 75% of PVOD patients, but may also be present in idiopathic PAH (15%).[2] Additionally, the absence of radiological abnormalities on HRCT does not definitively rule out PVOD.[2]

Ventilation/perfusion (V/Q) lung scan is recommended by guidelines as a routine investigation in the diagnostic workup of PH to detect chronic thromboembolic disease. Although it has been suggested that unmatched perfusion defects may also be found in PVOD, a recent study demonstrated that V/Q lung scans in patients with PVOD are comparable to what is usually observed in idiopathic and heritable PAH.[25]

Lung Function, Gas Exchange, and Exercise Testing

With the exception of occlusive venopathy associated with respiratory diseases, PVOD patients generally have normal spirometry and lung volumes on pulmonary function tests.[2] A severe reduction in diffusion capacity for carbon monoxide (DLCO) lower than 50% of predicted value is common in PVOD, in contrast to idiopathic or heritable PAH, where DLCO is relatively preserved for a long time.[2,26] The lower DLCO may be explained by a greater reduction in capillary blood volume from a compromised pulmonary vascular bed. Accordingly, arterial blood gas analysis typically reveals major resting hypoxemia in PVOD.[2]

Furthermore, oxygen desaturation nadir during the 6-minute walk test (6MWT) has been shown to be consistently lower in PVOD compared with PAH.[2] The physiological response during cardiopulmonary exercise testing in PVOD was reported in a homogeneous group of PVOD patients harboring *EIF2AK4* biallelic mutations.[27] These PVOD patients had lower peak oxygen consumption, greater oxygen desaturation during exercise, greater ventilatory inefficiency, higher dead-space ventilation at peak exercise, and greater dyspnea intensity, as compared to PAH patients.[27]

Bronchoalveolar Lavage

Bronchoscopy is not a routine investigation in PAH, but there may be a role for bronchoalveolar lavage (BAL) in patients with suspected PVOD.[28] It has been described that bronchoscopic airway inspection may show hyperemia of the lobar and segmental bronchi due to vascular engorgement.[29] Compared with PAH, Rabiller et al found a significantly elevated percentage of hemosiderin-laden macrophages and a higher Golde score, in keeping with the hypothesis of an occult alveolar hemorrhage in PVOD.[28] However, severe hypoxemia usually limits the interest in performing BAL in the diagnosis of PVOD.

These findings suggest that noninvasive testing could be helpful in the diagnosis of PVOD in patients with precapillary PH. A low resting PaO_2, low

SpO_2 during 6MWT, low DLCO, presence of an occult alveolar hemorrhage, and radiologic abnormalities on HRCT of the chest may identify a subgroup of patients with a high probability of PVOD, avoiding the need for hazardous and invasive surgical procedures in these patients.

MANAGEMENT

In contrast to PAH, randomized controlled trials are lacking in PVOD, and there remains no medical therapy with proven efficacy. Excluding lung transplantation, treatment options are unfortunately limited in PVOD, highlighting the importance of early noninvasive screening and consideration of referral for lung transplantation early in the course of the disease.

General and Supportive Measures

Severe resting hypoxemia and exertional desaturation are frequently observed in PVOD patients, justifying oxygen therapy to prevent further aggravation of PH from hypoxic pulmonary vasoconstriction. Conventional therapy includes high-dose diuretics to decrease the risk of pulmonary edema. Even if there are no specific data in PVOD, a rationale for anticoagulation exists because of risk for subsequent in situ thrombosis.[3] Recent ESC/ERS guidelines concluded that evidence of benefit for oral anticoagulation is confined to patients with idiopathic PAH, heritable PAH, and PAH due to anorexigens. No recommendation of anticoagulation has been proposed for PVOD.[9]

No evidence supports a possible role of immunosuppressive therapy in PVOD except for that which is associated with connective tissue disease.[30] Specifically, PAH patients with mixed connective tissue disease and systemic lupus erythematous (but not scleroderma) may improve with immunosuppressive therapy.[31,32]

PAH-Specific Therapy

The major concern with the use of PAH-specific therapy in PVOD is the risk of severe pulmonary edema, which has been reported with all PAH therapies (prostacyclin and its derivatives, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and calcium channel blockers).[2,33] The mechanism is understood to be due to the relative vasodilatation of the precapillary vessels exceeding that of the pulmonary capillaries and veins, associated with an increase in pulmonary blood flow, an increase in transcapillary hydrostatic pressure, and transudation of fluid into the pulmonary interstitium. Prevalence of pulmonary edema following initiation of pulmonary vasodilators is very high with calcium channel blockers and occurs in up to 50% of patients with PAH-specific therapies.[2,21,34] Nevertheless, clinical improvement or stabilization has been reported with continuous intravenous epoprostenol, iloprost, bosentan, and sildenafil.[7,35-46] Clinical trial evidence of benefit with these therapies in patients with PVOD is lacking, and long-term response to PAH-specific therapies remains rare.

Lung Transplantation

Lung transplantation remains the treatment of choice for PVOD and offers the possibility of cure for the disease. Because of the worse prognosis of PVOD patients and risk of pulmonary edema with PAH-specific therapies, early referral for transplantation should be considered at the time of diagnosis for eligible patients. To date, no histologically proven recurrence of PVOD after lung transplantation has been reported.

CONCLUSION

PVOD is a rare form of PH, but its clinical recognition is essential to propose adapted management of the disease. Diagnosis remains challenging, but arterial blood gases (hypoxemia), DLCO (severe reduction), HRCT (septal lines, ground-glass opacities, and lymph node enlargement) are useful to screen these patients. The recent discovery of biallelic mutations of the *EIF2AK4* gene in heritable disease will help to better understand pathophysiology of PVOD. Benefits of PAH-specific therapies remain to be demonstrated, and lung transplantation is the current therapy of choice for eligible patients with PVOD.

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