Pulmonary Veno-Occlusive Disease: An 80-Year-Old Mystery

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Introduction

Pulmonary arterial hypertension (PAH) is a severe entity characterized by elevated pulmonary artery (PA) pressure which frequently leads to right heart failure and death [1, 2]. Besides conventional therapies, several targeted vasodilators have been developed for PAH in relation to the molecular pathways in PA constriction [3]. Despite the recent progress in PAH treatment, there is still no established curative medical therapy and thus these patients have a poor prognosis [1, 4]. Pulmonary veno-occlusive disease (PVOD) is a rare disease related to PAH. Unlike PAH, PVOD affects the postcapillary venous vessels [5] and presents a worse outcome [6, 7]. Some studies have suggested that PVOD and PAH, along with pulmonary capillary hemangiomatosis (PCH), may represent different phenotypic manifestations of a spectrum of a single disease [4, 5, 8]. Because of pathological and clinical differences compared to other PAHs, PVOD together with PCH were categorized into a separate but associated group in relation to PAH, i.e. group 1’, in the 4th World Symposium on Pulmonary Hypertension held in Dana Point, Calif., USA [2].

Although 8 decades have passed since the first description by Dr. Julius Höra [9] in 1934, PVOD remains poorly understood, especially in terms of its pathogenesis and treatment. Most of the insights into this disease have been
obtained via single case reports and a few retrospective studies of case series. With difficulty, our knowledge regarding this entity has been gradually increasing thanks to investigators’ persistent efforts. This review summarizes the current knowledge on PVOD, with a special focus on recent progress.

**Epidemiology**

The incidence and prevalence of PVOD are not clearly known. This is not only because it is rarely reported but also because it is often misdiagnosed as precapillary pulmonary hypertension. PVOD accounts for approximately 10% of patients diagnosed with idiopathic PAH [10–12]. Thus, the annual incidence is estimated to be about 0.1–0.2 cases per million in the general population [10–12]. This number, however, may be underestimated because PVOD is also misdiagnosed as other forms of pulmonary hypertension, such as chronic thromboembolic pulmonary hypertension. In contrast to idiopathic PAH, which predominantly affects females, PVOD occurs almost equally in males and females [6, 7, 13, 14]. The age at diagnosis presents a wide range, from immediately after birth to the 7th decade of life.

**Etiology**

The etiology of PVOD remains largely unclear because many factors, such as the complexity of the disease and the difficulty of obtaining a biopsy due to the position of the lesion sites, have prevented researchers from studying this entity. There is no clue suggesting that PVOD develops through a single etiology. It is known to be inherited, or associated with congenital heart diseases, or even acquired. In addition to previous case reports, recent case series have provided more information [6, 7].

**Genetic Factors**

Several publications reporting the occurrence of PVOD in siblings have suggested a genetic risk factor [13, 15]. Three decades after that hypothesis, Runo et al. [8] reported a germline mutation in the BMPR2 gene in a PVOD patient with a family history. Subsequently, mutations in the BMPR2 gene were reported in more patients [6]. Since mutations in the BMPR2 gene are also involved in PAH, a similarity between PAH and PVOD was suggested [2]. In a quite recent report, Eyries et al. [16], using whole-exome sequencing, detected recessive mutations in the EIF2AK4 gene that cosegregated with PVOD in all 13 families studied, as well as biallelic EIF2AK4 mutations in 5 of 20 sporadic PVOD cases.

**Epigenetic Factors**

Recently, Perros et al. [17] reported an epigenetic involvement in PVOD. The granulysin (GNLY) gene was shown to be hypermethylated in gDNA from the lungs and blood of patients with PVOD compared to patients with PAH. Consequent alterations in the circulating cytotoxic cell subpopulations were also observed, which might contribute not only to the understanding of the etiology but also to the development of diagnostic tools.

**Infection**

Infection has been hypothesized as a cause of PVOD since the first report, but this has not been supported by sufficient direct evidence. Flu-like symptoms [18], clinical features suggesting a recent infection of rubella [19], toxoplasma [20], and autoptic findings indicating a viral infection [21] have been noted in some patients. PVOD has also been reported in 2 human immunodeficiency virus-infected patients [22, 23].

**Toxic Exposures**

Anorexigen exposure is a risk factor for PAH [24], but it has been reported in only 1 PVOD case [6]. Instead, many patients have undergone chemotherapies for various malignancies before the diagnosis of PVOD, with regimens including cisplatin, bleomycin, mitomycin, BNCU, mechlorethamine, vincristine, procarbazine, and cyclophosphamide [25, 26]. Accumulating evidence suggests that PVOD is a complication of hematopoietic stem cell transplantation, both allogeneic and autologous, from bone marrow, peripheral blood, and cord blood [27–30]. It is worth discussing how much transplantation itself contributes to PVOD, because chemotherapy, as mentioned above, and radiation, as constituents of the pretreatment for hematopoietic stem cell transplantation, have both been reported to be associated with PVOD [31]. The presence of a smoking habit is comparable between PVOD and idiopathic PAH patients [6, 32]; however, heavier smoking habits (more tobacco exposure) have been noted in PVOD compared to idiopathic PAH patients [6].

**Autoimmune Diseases**

Autoimmune diseases may cause thrombosis and tissue fibrosis, which could partially explain the pathologi-
These cases are also referred to as the pulmonary capillary hemangiomatosis (PCH) syndrome and partial anomalous pulmonary vein connection (PAPVC). These cases associated with systemic sclerosis, a spectrum of a single disease, are very diverse in their presentation, especially regarding their exact involvement in the etiology. The previously reported autoimmune diseases associated with PVOD are largely diverse and include focal granulomatous venulitis [33, 34], generalized venulitis such as in the setting of sarcoidosis or Langerhan’s cell granulomatosis [35–37], Sjögren’s syndrome [38], Felty’s syndrome [39], mixed connective tissue disease [40], systemic lupus erythematosus [41], Hashimoto’s thyroiditis [42], and limited or diffuse systemic sclerosis [43–45]. Gunther et al. [43] demonstrated in a recent study that, out of 26 precapillary pulmonary hypertension cases associated with systemic sclerosis, 16 (61.5%) presented ≥2 radiographic signs of PVOD on high-resolution computed tomography (HRCT). Interestingly, 8 of them experienced pulmonary edema after the initiation of PAH-targeted therapy. These results indicate that PVOD associated with scleroderma may be frequently misdiagnosed as PAH, suggesting the need for a cautious differential diagnosis when precapillary pulmonary hypertension is seen in a scleroderma patient.

Miscellaneous

Investigators have also reported other associations besides those mentioned above. Several infants with congenital heart disease, such as hypoplastic left heart syndrome and partial anomalous pulmonary vein connection, have been reported [46, 47]. These cases are considered to be due not only to the congenital obstruction of pulmonary venous return, because a case has been documented in association with unilateral pulmonary venous atresia occurring in the lung contralateral to PVOD [48]. A possible explanation could be the involvement of endothelial damage and coagulopathy, which is supported by 2 publications reporting 3 PVOD patients in association with oral contraceptives [49, 50], a description of PVOD in pregnancy [51], and other studies [27].

Pathology

As its name suggests, the histopathology of PVOD is represented by fibrous remodeling of the intima, which narrows or occludes small pulmonary veins or venules. The fibrous tissue could be either loose and edematous or dense and collagen rich. Large veins are sometimes affected, although not as frequently as small ones [14]. The media of the affected veins may present a normal thickness or show arteriolarization resulting from smooth muscle hypertrophy and an increase in elastic fiber. Calcium-encrusted elastic fiber may also be seen in some cases [52]. Recognizable thrombi or intraluminal fibrous septa suggestive of recanalization are observable in most cases.

Despite the ‘venous’ in its name, PVOD often exhibits lesions in pulmonary capillaries and arterioles or arteries. Medial hypertrophy and intimal fibrosis may be present in small arteries, mimicking PAH. However, plexiform lesions, a characteristic finding in idiopathic PAH, are usually absent [10–12, 53]. In some cases, alveolar capillaries may demonstrate dilation and congestion, resulting in an angioma-like appearance [52]. It is noteworthy that PCH can be distinguished from PVOD by its disordered capillary proliferation and the absence of venous lesions. Interestingly, a recent report by Lantuejoul et al. [5] demonstrated that, in a review of specimens from 35 previously diagnosed PVOD or PCH patients, 73% of the diagnosed PVOD patients and 80% of the diagnosed PCH cases exhibited each other’s histopathological features. These findings support the hypothesis that PVOD and PCH may represent 2 phenotypic manifestations of a spectrum of a single disease [2].

With a focus on lymphoid tissue, Thomas de Montpreville et al. [54] reported that lymphatic congestion, vascular transformation of the sinuses, intrasinusal hemorrhage with erythrophagocytosis and lymphoid follicular hyperplasia occur more frequently in PVOD than in pulmonary hypertension of other causes.

Other commonly observed lesions are interstitial edema and fibrosis. Hemorrhage may also be found in and around these areas, along with hemosiderotic changes [14]. Hemorrhage is of diagnostic importance because it allows detection of the disease by bronchoalveolar lavage (BAL) [32], which will be discussed below.

Clinical Features and Diagnosis

It is impossible to diagnose PVOD only based on its symptoms. Patients present with nonspecific symptoms that are also observed in PAH of other causes. Most patients complain of dyspnea on exertion. Some patients suffer from chest pain, cough (which is often nonproductive), cyanosis, and, rarely, syncope [5, 7]. Hemoptysis occurred in 8 out of 20 patients in a case series [5] but in only 1 out of 24 patients in another series [6]. Jones et al. [37] described a sarcoidosis-associated patient with hemoptysis in detail. Patients who develop right heart failure may present with lower extremity edema, a prominent P2 component of the 2nd heart sound, and a murmur of tricuspid regurgitation [7]. Crackles on chest
auscultation may indicate pulmonary infiltrates [10]. Clubbing was once thought to be more associated with PVOD than with PAH [7]. A recent study confirmed this tendency, but without statistical significance [6]. Orthopnea has also been reported in PVOD, though it is uncommon in other forms of PAH [7]. Pleural effusion was thought to be more frequent in PVOD than in other PAH a decade ago, but this was disproved by recent studies using HRCT [6, 55].

Diagnostic Approach

A definitive diagnosis of PVOD requires a surgical biopsy, which is an invasive, and dangerous procedure. Thus, clinicians often avoid this procedure and seek alternative methods. Fortunately, the diagnostic value of HRCT, pulmonary function tests, BAL, and flow cytometry for detecting alterations in cytotoxic cell subpopulations in PVOD is in the process of being established.

Right Heart Catheterization

Since PVOD shares many symptoms with PAH, clinicians seldom suspect PVOD immediately. A right heart catheterization is always performed to examine the hemodynamics, in which pulmonary hypertension is diagnosed by a mean PA pressure ≥25 mm Hg at rest. The pulmonary wedge pressure (PWP) in PVOD remains within the normal range (≤15 mm Hg) or is slightly elevated [6, 7]. It is these hemodynamic characteristics, along with the symptoms, that lead to the misdiagnosis of PAH. However, one may argue that this precapillary pattern is discrepant with the post-capillary lesions in PVOD. A widely accepted theory is that the PWP reflects the pressure in relatively large veins of a diameter similar to that of the occluded PA. These veins are usually larger than, and distal from, the affected small veins and therefore have normal pressures [56]. In light of this explanation, patients with a slightly elevated PWP may develop large vein lesions. An elevated true capillary pressure (not PWP) may be useful in the diagnosis of PVOD. However, 30 years after the establishment of the calculation principle [57], the estimation of true capillary pressure is still not applied clinically, with the exception of a few studies.

Radiology

Though less informative compared to computed tomography, chest radiography is still routinely done in patients suspected of having pulmonary hypertension. In addition to the common findings suggesting pulmonary hypertension, such as right ventricular enlargement and PA dilation, chest radiographs in PVOD may show Kerley B lines and a normal left atrium, distinguishing it from pulmonary hypertension owing to left heart disease [58].

HRCT is the most important imaging modality to discern between PVOD and PAH. Consistent with chest radiographs, chest HRCT demonstrates right ventricular hypertrophy and PA dilation in most patients [55, 59]. The triad of ground-glass opacities, particularly with a centrilobular pattern, thickened interlobular septa, and mediastinal lymphadenopathy, suggests PVOD rather than PAH with a high sensitivity and specificity [55] (fig. 1). Montani et al. [6] reported that the presence of 2 or more of the abnormalities listed above is 75% sensitive and 85% specific for the detection of PVOD in patients with presumed PAH. Concerning the size of the centrilobular ground-glass opacities, Miura et al. [60] demonstrated in a recent publication that smaller ground-glass opacities might differentiate PVOD from PCH. In addition, the presence of pleural effusion and pericardial effusion is comparable between PVOD and PAH [55].

As stated in recent European Respiratory Society/European Society of Cardiology guidelines [4], unmatched perfusion defects on ventilation/perfusion scans may also occur in PVOD, like in chronic thromboembolic pulmonary hypertension. This is not a common finding in
PVOD (about 7%) [7, 61] and was recently detected to occur in PAH as well, with an incidence comparable to that in PVOD [61]. The guidelines call attention to the possibility that PVOD is sometimes misdiagnosed as chronic thromboembolic pulmonary hypertension, rather than suggesting the diagnostic value of ventilation/perfusion scans in PVOD.

**Pulmonary Function Tests**

A decreased diffusion capacity for carbon monoxide (DLCO) has been described not only in PAH but also in PVOD [62]. Based on a case series of 24 PVOD patients, Montani et al. [6] concluded that the DLCO and the DLCO/alveolar volume ratio were decreased in both PVOD and PAH and were significantly lower in PVOD. Some patients may present restrictive ventilatory defects [7]. The case series mentioned above, however, showed that the averages of the forced expiratory volume in 1 s (FEV1) and the FEV1/vital capacity ratio were within the normal ranges and were comparable to those in PAH [6].

**BAL**

Considering the alveolar hemorrhage on histological examination, Rabiller et al. [32] performed BAL in 8 PVOD and 11 idiopathic PAH patients without hemoptysis with the hypothesis that PVOD patients may have occult alveolar hemorrhage. The Golde score was used to assess the alveolar hemorrhage; 200–300 macrophages were counted and each cell was graded for hemosiderin on a scale of 0–4. A mean score for 100 cells was used, with 0 being the minimum and 400 the maximum score, and scores between 0 and 20 were considered normal [63]. In the subsequent cytological analyses, the BAL fluid of PVOD patients was characterized by a higher percentage of hemosiderin-laden macrophages and, consequently, an elevated Golde score, indicating occult alveolar hemorrhage. Only 1 idiopathic PAH patient exhibited an elevated Golde score. In contrast, only 1 PVOD patient had a Golde score within the normal range. This study suggested the possible application of BAL in the diagnosis of PVOD, which had a sensitivity of 88% and a specificity of 91% when the Golde score cutoff was set at 20. A successful application in a suspected case was reported afterwards [64].

**Flow Cytometry**

In a recent publication, Perros et al. [17] reported that the G3NY gene was hypermethylated in gDNA from the lungs and blood of patients with PVOD compared to patients with PAH, which was associated with alterations in cytotoxic cell subpopulations. The study uncovered a new pathway in the etiology of PVOD and indicated a new diagnostic technique. However, the complicated alterations in cytotoxic cell subpopulations made it difficult to define criteria to differentiate PVOD from PAH by flow cytometry analyses. In order to obtain sufficient data and evidence, future research is still required.

**Other Findings of Diagnostic Usefulness**

Studies have also shown a reduced partial pressure of arterial oxygen (PaO2) in PVOD (even lower than that in PAH) [6, 7]. In addition, during the 6-min walk test, rather than the distance, a lower nadir arterial oxygen saturation measured by pulse oxymetry could be of diagnostic value [6]. Acute vasodilator testing is useful in predicting the response to treatment in PAH [1, 4] but may cause pulmonary edema in PVOD [7] and thus needs to be carefully conducted. Pulmonary edema could also develop after the initiation of vasodilators, including calcium channel blockers (CCBs), bosentan, epoprostenol, and sildenafil, in nearly one half of patients [6, 7, 56]. Acute pulmonary edema after administration of these agents in a patient suspected of having PAH is a clue for the clinician to doubt his/her diagnosis and reevaluate the patient for PVOD, like Masters and Bennett [65] did.

**Prognosis and Treatments**

The prognosis of PVOD is dismal, with a reported 1-year mortality rate of 72% [7]. Most patients die within 2 years of the diagnosis [66]. A recent report described the longest survival, i.e. >15 years after the initial admission [67]. Montani et al. [6] compared PVOD and PAH patients with similar baseline hemodynamic and 6-min walk test findings and New York Heart Association (NYHA) functional classes and found that PVOD patients had extremely worse outcomes compared to PAH patients. In recent years, physicians have reported progress in treating PVOD in single case reports or case series. Despite those efforts, lung transplantation remains the only cure, and an early decision of transplantation is considered crucial.

**Conventional Therapies**

Continuous oxygen therapy is a class I recommendation for PAH patients whose PaO2 is consistently <60 mm Hg (8.0 kPa) [4]. Clinicians consider the initiation of oxygen as treatment for the symptoms of PVOD, as well as to prevent exacerbations [56]. Although we should not...
ignore the lack of evidence indicating a mortality benefit of oxygen therapy, this choice is never wrong since the adverse effects are few.

Idiopathic PAH patients benefit from oral anticoagulants due to their effect against thrombotic lesions [68]. Guidelines recommend PAH patients who receive intravenous (i.v.) prostacyclins to undergo anticoagulation in the absence of contraindications [4]. Although there are no data regarding anticoagulation in PVOD, the use of warfarin has been adopted from PAH guidelines because obvious or recanalized thrombi are seen in the pathology of PVOD, like in idiopathic PAH [14]. However, a recent study emphasizing the occult alveolar hemorrhage in PVOD urged physicians to be cautious when subscribing warfarin [32].

**PAH-Targeted Therapies**

PAH-targeted therapies such as CCBs, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclins have an established and important role in the treatment of PAH [4]. However, these cannot be simply applied in the treatment of PVOD because of the lack of evidence as well as the reports of adverse effects, like pulmonary edema, after the initiation of these agents. Theoretically, when the pulmonary arterioles dilate and the resistance of the pulmonary veins remains fixed, the transcapillary hydrostatic pressure might increase and pulmonary edema may occur. As a result, the European Respiratory Society/European Society of Cardiology guidelines recommend management in centers with extensive experience when administering these agents (class IIa, level C) [4]. The recently reported cases on the use of these therapies in PVOD have provided slightly more information.

CCBs, such as nifedipine, are widely prescribed in cases of systemic hypertension as well as in PAH patients presenting with a positive acute vasodilator response. In PVOD, their use has been reported in only a few publications. Salzman and Rosa [69] documented a long survival with nifedipine. In the case series reported by Holcomb et al. [7], of 8 patients who were on CCBs, only 1 had sustained clinical improvement but 6 experienced pulmonary edema. Montani et al. [6] also reported that 1 out of 24 patient experienced pulmonary edema. Based on these publications, CCBs appear not to be a good choice. However, the documented cases are few and the conditions are varies. Like with epoprostenol (described below), cautious administration might help.

Epoprostenol is a powerful agent in the treatment of PAH and it has been proven to improve survival in idiopathic PAH in randomized trials [4]. Among the vasodilators, epoprostenol has the most accumulated evidence in the management of PVOD. It was reported to cause pulmonary edema in one case in 1998 [70]. Holcomb et al. [7] demonstrated that, of 3 patients receiving i.v. epoprostenol, 1 developed pulmonary edema. Furthermore, Montani et al. [6] reported that, of 11 patients taking epoprostenol, 5 experienced episodes of pulmonary edema. In spite of the probability of developing pulmonary edema of approximately 40%, physicians have few choices for the treatment of PVOD and have to prescribe epoprostenol in some conditions. Fortunately, 2 recent studies indicated its safety and efficacy when used with caution. Montani et al. [71] reported in 2009 that, among 12 PVOD patients undergoing i.v. epoprostenol therapy with slow dose increases and high doses of diuretics, only 1 developed mild reversible pulmonary edema in the following 3–4 months. Improvement was observed in the NYHA functional class and cardiac index but not in the 6-min walk test. Nine patients were successfully bridged to lung transplantation. Quite recently, Ogawa et al. [72] documented 6 PVOD patients and 2 PCH patients undergoing i.v. epoprostenol treatment. With cautious observation, the authors stopped increasing the dose of epoprostenol and added diuretics or catecholamine when signs of deterioration such as pulmonary edema were noticed. The subjects showed temporary improvement in their NYHA functional class, 6-min walk distance, plasma brain natriuretic peptide level, and cardiac index, but not in their PA pressure or pulmonary vascular resistance. Epoprostenol worked as a bridge to lung transplantation in 4 subjects, 3 of whom had PVOD. As indicated by these studies, epoprostenol may result in improvement for a short time, but its long-term efficacy is still unknown. The current opinion, therefore, is that it may at least be safely used with intensive observation as a bridge to transplantation.

Bosentan, an endothelin receptor antagonist, has been reported to achieve improvement in very few cases [64, 73]. However, it is also on the list of agents which produce pulmonary edema at a rate of 33% (2 out of 6 patients) [6]. Ye et al. [73] reported one patient in whom the use of bosentan turned out to be safe and effective when administered with diuretics. Sildenafil, a phosphodiesterase type 5 inhibitor, has even less reported evidence. It has been demonstrated to be effective in only 3 cases to date [74–76]. In addition, Montani et al. [77] observed an exacerbation of symptoms and the occurrence of pulmonary edema after the administration of sildenafil in addition to bosentan in a patient and recommended close
monitoring and the use of diuretics to reduce the risk. Other new PAH-targeted therapies, such as tadalafil, have not been reported in PVOD yet.

Pulmonary edema is the largest obstacle for the employment of PAH-targeted agents in PVOD. However, no clinical, functional, or hemodynamic characteristics have been proven to predict the development of pulmonary edema [6].

**Immunosuppressive Agents**

Immunosuppressive medications, such as glucocorticoids and antimetabolites, may result in the clinical improvement of PAH associated with connective tissue disease [4]. They have also been employed in PVOD, particularly among patients with autoimmune diseases, resulting in clinical improvement [37, 38, 45, 78]. However, the experiences have been poor and, more importantly, no data support the wide use of these agents in PVOD in the absence of autoimmune diseases.

**Lung Transplantation**

Lung transplantation is considered the only cure for PVOD, as in PAH. Thus, the guidelines recommend a referral to a transplant center as soon as a proper diagnosis is established [4]. Although there is only one report of recurrence after heart-lung transplantation in a 26-year-old man [79], no further such cases have been documented.

To bridge patients to transplantation, besides the medications described above, surgical and mechanical support may also be useful. Strueber et al. [80] demonstrated that a lung assist device connected via the PA main trunk and left atrium successfully bridged 4 patients to bilateral lung transplantation or heart-lung transplantation. Hoopes et al. [81] recently developed combined atrial septostomy and venovenous extracorporeal membrane oxygenation as a mechanical support, which resulted in hemodynamic stabilization in a patient.

**Other Medications**

In hepatic veno-occlusive disease, defibrotide is used successfully as an investigational drug. It produces a favorable response in patients with hepatic veno-occlusive disease after stem cell transplantation and even has prophylactic effects [82, 83]. Defibrotide works via heterogeneous effects on blood coagulation and fibrinolysis. Because of the lack of evidence, its use is not recommended in PVOD [10]. Nevertheless, one case report from Willems et al. [84] suggested its potential benefits in PVOD, but this still requires further investigation.

As indicated by several recent trials [85, 86], imatinib may improve the exercise capacity and hemodynamics as an add-on therapy in PAH, possibly through the inhibition of platelet-derived growth factor receptor. In PVOD, the involvement of platelet-derived growth factor is unknown, and the evidence remains controversial. Overbeek et al. [87] reported a patient who experienced rapid relief of symptoms after the addition of imatinib to epoprostenol. On the contrary, Koiwa et al. [88] described a case that was refractory to imatinib. Kataoka et al. [89] reported another case which did not respond to imatinib but did improve with sorafenib, a multikinase inhibitor which is usually used in the treatment of kidney cancer.

**Conclusions and Future Perspectives**

PVOD is still a rare and poorly understood subgroup of pulmonary hypertension despite investigators’ persistent efforts over the past 8 decades. PAH-targeted therapies are currently applied in PVOD with caution, although the evidence is still not sufficient. Their limited benefit and the risk of pulmonary edema leave lung transplantation as the only cure. The prognosis is still poor, emphasizing the importance of an early diagnosis. Fortunately, several diagnostic tools have been developed, among which HRCT has the most clinical importance. By optimizing these tools, clinicians are expected to be able to reduce the incidence of misdiagnosis of PVOD. Future studies are required to further elucidate the underlying etiology or etiologies, as well as to determine optimal therapies.

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