

Case report

Pulmonary veno-occlusive disease, a rare but fatal complication among patients with hematologic malignancy

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Abstract:

Pulmonary veno-occlusive disease (PVOD), classified as group 1 pulmonary hypertension, is a rare but fatal form of pulmonary artery hypertension (PAH) manifesting subacute to chronic progressive dyspnea due to the increase in pulmonary arterial pressure and right-side heart failure. Exposure to chemotherapy and poststem cell transplantation constitute risk factors of PVOD. We herein demonstrate a case of PVOD in a middle-aged female with the underlying disease of T-cell/histiocyte-rich large B cell lymphoma treated using an alkylating agent and hematopoietic stem cell transplantation and presenting biventricular heart failure. After being treated using methylprednisolone, diuresis and pulmonary vasodilators, her clinical symptoms transiently improved. Unfortunately, the patient passed away one year after the diagnosis due to the progression of right-sided heart failure. Necropsy of the lung was performed revealing the occlusion of pulmonary venules.

Keywords : ● Pulmonary veno-occlusive disease ● Hematopoietic stem cell transplantation
● Alkylating agent

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รายงานผู้ป่วย

ภาวะอุดกั้นของเส้นเลือดดำจากปอดในผู้ป่วยมะเร็งทางโลหิตวิทยา

ภายหลังได้รับยาเคมีบำบัดและการปลูกถ่ายเซลล์ต้นกำเนิด

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บทคัดย่อ

ภาวะอุดกั้นของเส้นเลือดดำจากปอดหรือ pulmonary veno-occlusive disease (PVOD) เป็นภาวะที่พบบได้น้อยแต่มีความรุนแรงสูง ภาวะดังกล่าวถูกจัดเป็นกลุ่มที่ 1 จากทั้งหมด 5 กลุ่มของภาวะความดันหลอดเลือดปอดสูง (pulmonary hypertension) ซึ่งมีอาการทางคลินิกของภาวะหายใจลำบากแบบกึ่งเฉียบพลันถึงเรื้อรัง เนื่องจากการเพิ่มขึ้นของความดันโลหิตในหลอดเลือดแดงปอด และภาวะหัวใจด้านขวาล้มเหลว การได้รับเคมีบำบัดและการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด นับเป็นหนึ่งในปัจจัยเสี่ยงของภาวะอุดกั้นของเส้นเลือดดำจากปอด ด้วยเหตุนี้ทางคณะผู้รายงานจึงได้รายงานตัวอย่างผู้ป่วยหญิงไทยวัยกลางคน มาด้วยอาการหายใจลำบากและหัวใจล้มเหลวภายหลังจากการรักษาโรคมะเร็งต่อมน้ำเหลืองชนิด T-cell/histiocyte-rich large B cell lymphoma ด้วยยาเคมีบำบัดและการปลูกถ่ายเซลล์ต้นกำเนิด ผู้ป่วยได้รับการวินิจฉัยเป็นภาวะอุดกั้นของเส้นเลือดดำจากปอด หลังได้รับการรักษาด้วยยาคอร์ติโคสเตียรอยด์ ยาขับปัสสาวะ และยาขยายหลอดเลือดจากปอดผู้ป่วยอาการดีขึ้นเพียงชั่วคราวและเสียชีวิตหลังการวินิจฉัย 1 ปีเนื่องจากความรุนแรงของภาวะหัวใจด้านขวาล้มเหลวที่มากขึ้น ผลการชันสูตรชันเนื่องจากปอดแสดงให้เห็นการอุดตันของเส้นเลือดดำขนาดเล็กซึ่งเข้าได้กับภาวะอุดกั้นของเส้นเลือดดำจากปอด

คำสำคัญ : ● ภาวะอุดกั้นของเส้นเลือดดำจากปอด ● การปลูกถ่ายเซลล์ต้นกำเนิด ● ยาเคมีบำบัดกลุ่มแอลคิเลท

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:155-62.

Introduction

Pulmonary hypertension (PH) is a pathophysiologic condition of the pulmonary circulation defined by a mean pulmonary artery pressure (mPAP) > 20 mmHg. Pulmonary veno-occlusive disease (PVOD) is a rare cause of PH predominantly involving pulmonary venules.¹ Veno-occlusive disease is one of the most serious complications following hematopoietic stem cell transplantation (HSCT). Endothelial damage may explain the pathophysiology of these clinical syndromes. Although PVOD is less common than hepatic VOD, the prognosis of PVOD is worse.² We present a case of PVOD, possibly due to chemotherapy exposure and autologous stem cell transplantation, in a middle-aged female with underlying disease T-cell/histiocyte-rich large B-cell lymphoma (TCHRBCL).

Case presentation

A 60-year-old female received a diagnosis of T-cell/histiocyte-rich large B-cell lymphoma (TCHRBCL) stage IVAE two years ago. She finished treatment involving six cycles of an R-CHOP regimen including rituximab 375 mg/m², vincristine 1.4 mg/m² and cyclophosphamide 750 mg/m² on day 1 and prednisolone 100 mg/d on days 1 to 5; the positron emission tomography/computed tomography (PET/CT) showed a complete metabolic response. Six months later (12 months before admission), the lymphoma relapsed in the central nervous system, diagnosed by a surveillance PET/CT, without any neurological symptoms. She was treated with six cycles of HDMTX-ifosfamide regimen including methotrexate 4 mg/m² on day 1, ifosfamide 1.5 g/m² on days 3 to 5 and dexamethasone 10 mg/d on days 1 to 3. At the end of treatment, magnetic resonance imaging (MRI) showed decreased size and enhanced infiltrative brain parenchymal lesion compatible with partial response. She underwent whole brain radiotherapy 30.6 Gy in 17 fractions with boost radiotherapy 45 Gy in 25 fractions at the residual tumor and proceeded to stem cell mobilization with high dose cyclophosphamide 3 g/m². Four months before this admission, an

autologous peripheral blood stem cell transplantation was performed using carmustine (BCNU) 400 mg/m² and thiotepea 5 mg/kg/d for two days as a conditioning regimen. Without any major complications during the transplantation periods, the engraftment of hematopoietic stem cells occurred on day 10 after stem cell infusion. The disease evaluation using an MRI of the brain three months after transplantation showed complete remission. At 4 months posttransplant, she came to an emergency department for shortness of breath with dry cough followed by paroxysmal nocturnal dyspnea and bilateral pedal edema for one month. Her body weight increased from 44 to 48 kilograms in two weeks. On physical examination at this admission, she was afebrile with a body temperature of 37 degrees Celsius, blood pressure of 114/71 mmHg, pulse rate of 104 bpm and respiratory rate of 18 breaths/minute with oxygen saturation of 95%. Signs of biventricular heart failure were noted including internal jugular venous engorgement up to the mandible, fine crepitation of both lower lungs and bilateral pedal edema. However, the heart size was normal with the point of maximal impulse (PMI) at the fifth intercostal space and the midclavicular line. No left or right ventricular heaving was observed on palpation. Signs of pulmonary hypertension included the loud P2 and pansystolic murmur of grade II/VI at the left lower parasternal border with positive Carvallo's sign compatible with tricuspid valve regurgitation, and no enlargement of peripheral lymph nodes were found. Other physical examinations were unremarkable. In addition to the clinical of biventricular heart failure with signs of pulmonary hypertension, a chest X-ray showed enlargement of the right atrium, right ventricle, pulmonary arteries (Figure 1). The finding from 12-lead ECG was right axis deviation and poor R progression compatible with right ventricle strain pattern (Figure 2). The echocardiography report confirmed severe pulmonary hypertension with mean pulmonary artery pressure of 46 mmHg, moderate right ventricular dilatation and severely impaired right ventricular systolic function together with moderate tricuspid

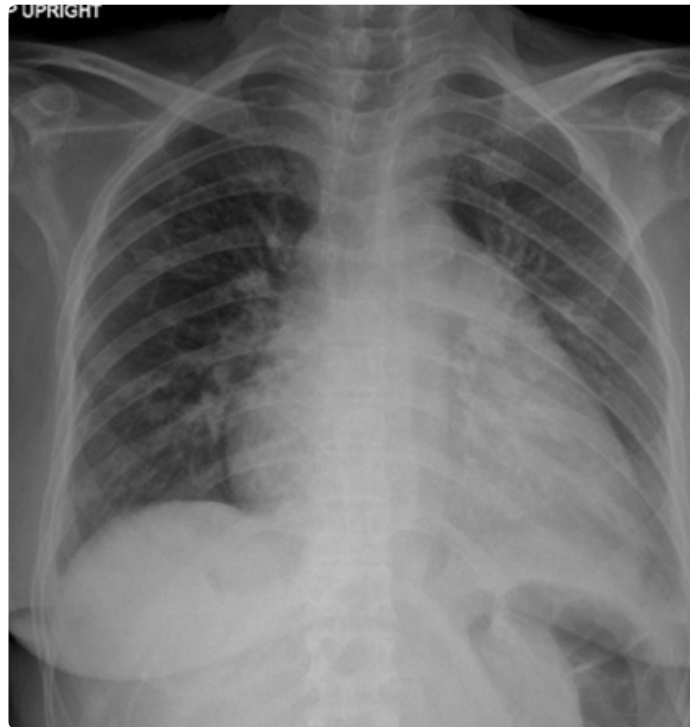


Figure 1 Chest X-ray showed enlargement of the right atrium, right ventricle, and pulmonary arteries.

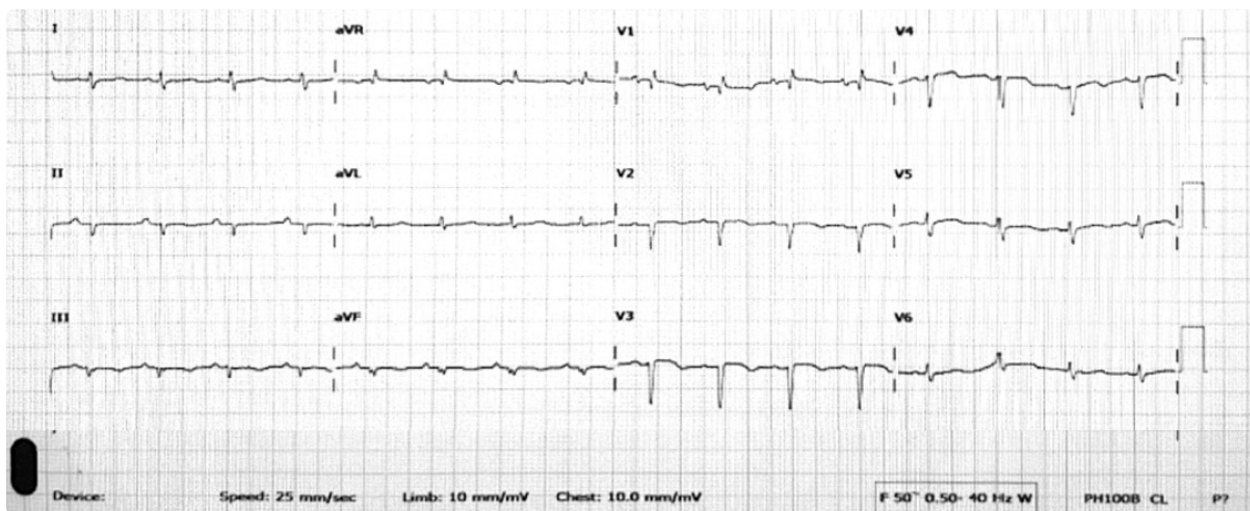


Figure 2 ECG 12 lead showed right axis deviation and poor R progression compatible with right ventricle strain pattern

regurgitation. However, normal left ventricular size and systolic function was observed with a left ventricular ejection fraction of 60%. To determine the etiology of pulmonary hypertension, CT of the pulmonary artery was performed showing an enlarged pulmonary trunk, cardiomegaly with a moderate amount of pericardial effusion and a concentric intraluminal filling defect in an artery of the posterior basal segment of the left lower lung, representing acute pulmonary embolism. Additionally, multifocal irregular consolidations, interlobular

septal thickening and ground glass opacities were noted in both lungs, more prominent in the lower lungs, with a moderate amount of bilateral pleural effusion (Figure 3). The pulmonary function test showed a moderately restrictive lung pattern without an obstructive pattern and a very low lung diffusing capacity for carbon monoxide (DLCO) which is disproportionate to the degree of pulmonary restriction representing pulmonary vascular disease (Figure 4). During admission, the Swan Ganz catheter was inserted, revealing normal pulmonary artery

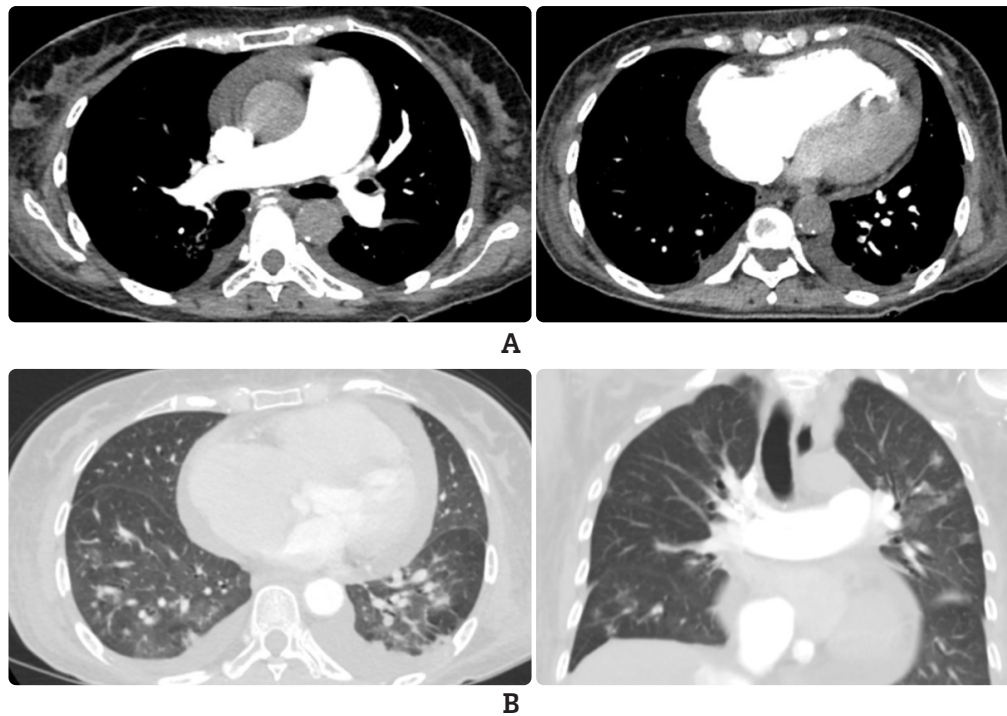


Figure 3 A) CTPA showed an enlarge pulmonary trunk, cardiomegaly with a moderate amount of pericardial effusion and there is a concentric intraluminal filling defect in an artery of posterior basal segment of left lower lung, representing acute pulmonary embolism. B) Lung window of the computed tomography showed multifocal irregular consolidations, interlobular septal thickening, and ground glass opacities in both lungs, more prominent in the lower lungs, with a moderate amount of bilateral pleural effusion

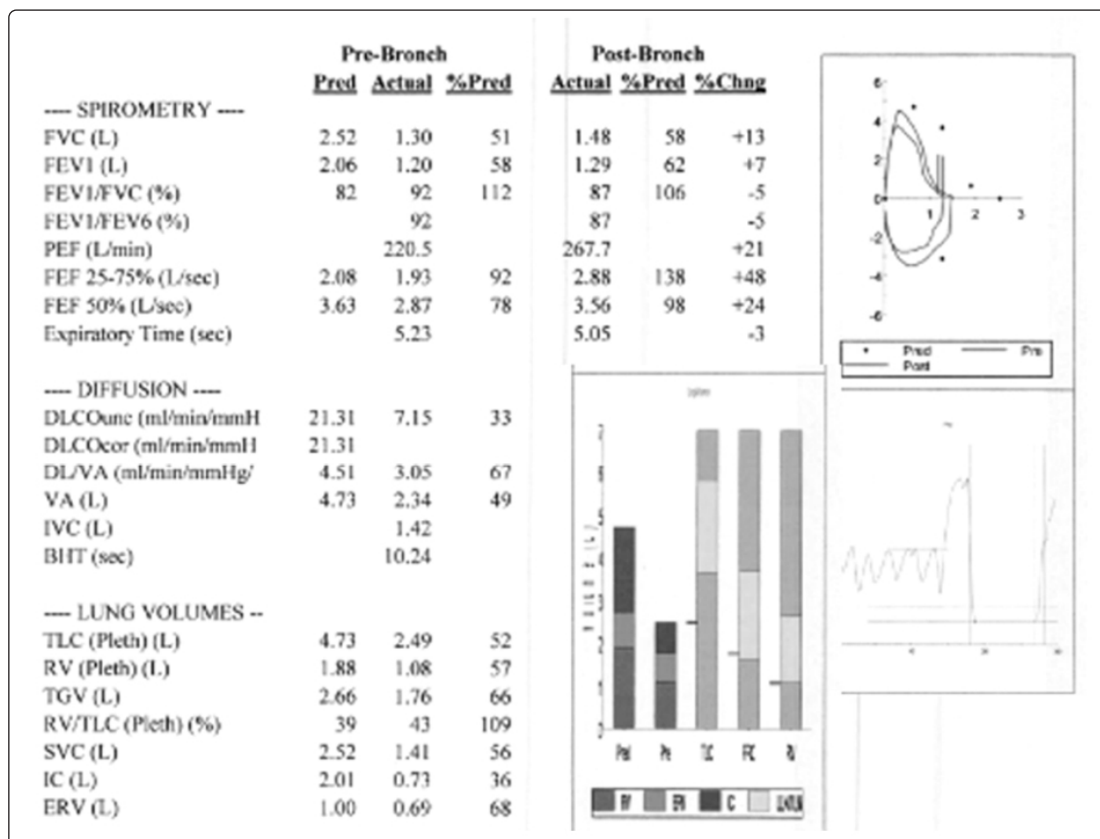


Figure 4 Pulmonary function test showed a moderately restrictive lung pattern without an obstructive pattern and a very low lung diffusing capacity for carbon monoxide (DLCO) representing pulmonary vascular disease

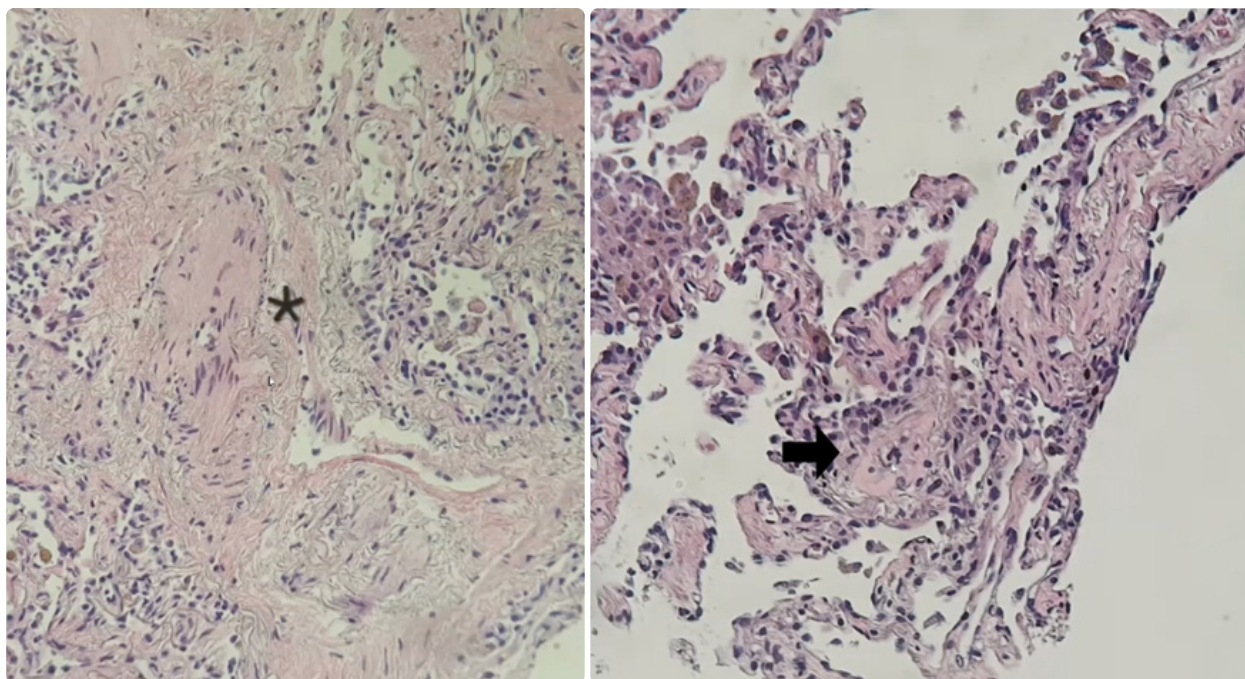


Figure 5 Pulmonary pathology demonstrated thickened intraacinar vessels in vein (starix) and small venule (arrow) with luminal narrowing

wedge pressure (PAWP) of 7 mmHg (in the euvoletic status). The differential diagnosis included drug-induced PVOD, chronic thromboembolic pulmonary hypertension or idiopathic pulmonary artery hypertension (PAH). Diuresis and pulmonary vasodilators were administered, and her clinical signs slowly improved. She was discharged home around two months after hospitalization. Unfortunately, the clinical of pulmonary hypertension worsened despite optimal pulmonary vasodilators and diuresis. She passed away one year after the onset of pulmonary hypertension. Necropsy of the lung was performed demonstrating thickened intra-acinar vessels, both vein and artery, supporting a diagnosis of PVOD (Figure 5).

Discussion

PVOD and pulmonary capillary hemangiomatosis, defined as group 1 in the current classification of pulmonary hypertension, are considered to be a similar entity.¹ The estimated annual incidence of PVOD is 0.1 to 0.2 cases per million in the general population. Still, the true incidence remains unknown.³ PVOD following bone marrow transplantation was first reported by Troussard

in 1984.⁴ The triad of severe PAH, radiographic evidence of pulmonary edema and normal PAWP are classically described clinical diagnostic criteria.² The pathologic hallmark is an obliteration of small pulmonary veins by fibrous intimal thickening and patchy capillary proliferation.⁵ PVOD contributed to a progressive increase in pulmonary vascular resistance, pulmonary vascular congestion, progressive dyspnea and right ventricular heart failure. A series of 11 patients with PVOD reported a mortality rate of 72% within one year of diagnosis.⁶ The pathogenesis of PVOD following HSCT has remained unclear. Some reported cases demonstrated the relationship between transplant-associated risk factors and developing PVOD. The underlying conditions preceding the transplant and subsequent PVOD were predominantly hematologic malignancies. From related case series, allogeneic stem cell transplants have a greater proportion of the disease than autologous stem cell transplants. The onset of PVOD typically occurs after several weeks to months following the transplant, although a minority of cases develop within days.² Chemotherapy exposure is a risk factor for PVOD. Thirty-seven cases of chemotherapy-associated PVOD were identified in the

French PH network and systematic literature analysis; the median age was 37.8 years (range, 2 to 66 years) and the median time from initiating chemotherapy to diagnosis was 4 months (range, 2 to 214 months). Exposure to alkylating agents was observed in 83.8% of cases, mostly represented by cyclophosphamide (43.2%). In animal models, cyclophosphamide was able to induce PH based on hemodynamic, morphologic, biological parameters and histopathologic assessment. Furthermore, carmustine had been used in 13.5% of PVOD cases in the same cohort. These demonstrated a plausible cause-effect relationship between alkylating agents and PVOD.⁷ Moreover, in some reports of pediatric patients undergoing HSCT, exposure to the conditioning regimen of busulfan, fludarabine and thiotepa (Bu/Flu/TT) was significantly associated with pulmonary hypertension. However, no definite cases of PVOD have been reported.⁸ Eukaryotic translation initiation factor 2 α kinase 4 (EIF2AK4) with an autosomal recessive transmission was the genetic predisposition of PVOD. Biallelic mutation of EIF2AK4 leading to impaired cellular stress response was found in nearly all hereditary PVOD and around 20% in sporadic PVOD.⁹ Unlike idiopathic PVOD, hereditary PVOD tends to occur at younger ages, specifically during the second to fourth decade of life.¹⁰ Though no evidence demonstrated an association between chemotherapy and EIF2AK4 mutation, these combined factors may increase the risk of PVOD. Similar to the systematic analysis, the presented case was diagnosed at age 60 and 2 years after receiving alkylating chemotherapy. According to the strong risk factor of receiving alkylating agents and the patient's age at diagnosis, genetic testing for EIF2AK4 mutation may not provide benefit. Lung or heart to lung transplantation remains the only definitive therapy offering a survival benefit among patients with PVOD. However, the pharmacologic treatment of the disease is challenging. From related case reports/series; some patients with PVOD taking pulmonary vasodilators showed an improvement in hemodynamics or stabilization of the disease course.¹¹ The prevalence

of pulmonary edema after vasodilator for PAH therapy among patients with PVOD may be as high as 75% for calcium channel blockers and up to 50% with targeted PAH drugs, e.g., epoprostenol and bosentan.^{6,12} Pulmonary vasodilators must be initiated with great caution among patients with PVOD and treatment should be conducted in a pulmonary vascular expertise center. Other treatment options including steroids, immunosuppression, anticoagulants and thrombolytics demonstrated variable treatment outcomes without proven efficacy. Oxygen therapy and optimal intravascular volume status are essential.

Conclusion

PVOD constitutes an uncommon form of PH. Chemotherapy especially alkylating agents and stem cell transplantation were considered risk factors. Clinical recognition and prompt investigation are crucial due to its dismal prognosis.

References

- Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, 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 Respir J*. 2015;46:903-75.
- Bunte MC, Patnaik MM, Pritzker MR, Burns LJ. Pulmonary veno-occlusive disease following hematopoietic stem cell transplantation: a rare model of endothelial dysfunction. *Bone Marrow Transplantation*. 2008;41:677-86.
- Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. *American journal of respiratory and critical care medicine*. 2006;173:1023-30.
- Troussard X, Bernaudo JF, Cordonnier C, Fleury J, Payen D, Briere J, et al. Pulmonary veno-occlusive disease after bone marrow transplantation. *Thorax*. 1984;39:956-7.
- Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. *Journal of the American College of Cardiology*. 2004;43(Suppl 12):25s-32s.

6. Holcomb BW, Jr., Loyd JE, Ely EW, Johnson J, Robbins IM. Pulmonary veno-occlusive disease: a case series and new observations. *Chest*. 2000;118:1671-9.
7. Ranchoux B, Gunther S, Quarck R, Chaumais MC, Dorfmueller P, Antigny F, et al. Chemotherapy-induced pulmonary hypertension: role of alkylating agents. *Am J Pathol*. 2015;185:356-71.
8. Levy M, Moshous D, Szezepanski I, Galmiche L, Castelle M, Lesage F, et al. Pulmonary hypertension after bone marrow transplantation in children. *Eur Respir J*. 2019;54.
9. Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet*. 2014;46:65-9.
10. Hadinnapola C, Bleda M, Haimel M, Screaton N, Swift A, Dorfmueller P, et al. Phenotypic Characterization of EIF2AK4 Mutation Carriers in a Large Cohort of Patients Diagnosed Clinically with Pulmonary Arterial Hypertension. *Circulation*. 2017;136:2022-33.
11. Montani D, Lau EM, Dorfmueller P, Girerd B, Jaïs X, Savale L, et al. Pulmonary veno-occlusive disease. *European Respiratory Journal*. 2016;47:1518.
12. Montani D, Achouh L, Dorfmueller P, Le Pavec J, Sztrymf B, Tchérakian C, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine*. 2008;87:220-33.