

## Pulmonary veno-occlusive disease: a case report and a review of therapeutic possibilities

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*Pulmonary veno-occlusive disease: a case report and a review of therapeutic possibilities. T.W. De Vries, J.J. Weening, R.J. Roorda.*

**ABSTRACT:** We describe the observation of a 12 yr old girl who died of pulmonary veno-occlusive disease (PVOD). Diagnosis was based on histological examination of an open lung biopsy. The differential diagnosis, pathogenesis and possible therapies are discussed. Although medical therapy can sometimes give some temporary relief, lung transplantation might offer these patients a better chance of survival and a better quality of life.

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Pulmonary veno-occlusive disease (PVOD) is a disease with pulmonary hypertension and impaired lung function [1]. The most prominent symptom is progressive dyspnoea. Some patients exhibit syncopes [2-4]. Physical examination reveals signs of chronic hypoxia and cor pulmonale. The onset of the disease is mostly during childhood or adolescence, but patients have been described who contracted the disease in middle age. The youngest patient reported was 3 weeks old [5], the oldest was a woman of 67 [3]. The definitive diagnosis is based on the histology of an open lung biopsy in combination with the clinical signs and symptoms [6, 7]. The disease is relatively rare, and its incidence is unknown; about 70 patients have been described in the literature [8-10]. PVOD is fatal within a few years after the onset of the symptoms. So far, no effective therapy has been found. Lung transplantation will probably give these patients a new prospective.

### Case report

The reported patient, a 12 yr old girl, had always been in excellent health until one year prior to admission. She then suffered from a lower respiratory tract infection, treated with antibiotics (amoxicillin). Her condition then slowly deteriorated; she suffered from progressive dyspnoea, and was finally confined to bed and needed supplementary oxygen treatment. She was admitted to another hospital where despite several diagnostic tests including open lung biopsy, no diagnosis could be made. She was therefore admitted to our department.

She had no fever and did not cough. There was no phlegm production or haemoptysis. She denied syncopes. Family history was negative for lung diseases and congenital cardiac malformations.

Physical examination revealed a dystrophic, dyspnoeic girl. Her height was 139 cm (less than third percentile, length for age) and her weight was 22 kg (less than third percentile, weight for height). Pulse rate was 120 beats·min<sup>-1</sup> regular, blood pressure was 100/75 mmHg. Frequency of breathing was 40 breaths·min<sup>-1</sup>. The patient showed sub- and intercostal retractions and central cyanosis despite being given 100% oxygen (2 l·min<sup>-1</sup>) continuously. There was marked clubbing of the fingers and toes. Breath sounds were normal; no crepitations were audible. A right ventricle impulse was palpable. The second heart sound was loud and not split. There were no cardiac murmurs. The liver was palpable 4 cm below the costal margin. The ankles were slightly oedematous.

Laboratory investigation showed elevated serum haemoglobin: 11.6 mmol·l<sup>-1</sup> (normal 8.1-9.9 mmol·l<sup>-1</sup>) and no signs of bacterial infection; total white blood cell count: 8.7×10<sup>9</sup>·l<sup>-1</sup> with normal cell differentiation; C-reactive protein: 3 mg·l<sup>-1</sup>. Arterial blood gas analysis (while breathing 100% oxygen 2 l·min<sup>-1</sup>) demonstrated severe hypoxaemia with hyperventilation and compensatory alkalosis: pH 7.40, oxygen tension (P<sub>O<sub>2</sub></sub>) 4.0 kPa, oxygen saturation 62%, carbon dioxide tension (P<sub>CO<sub>2</sub></sub>) 2.1 kPa, HCO<sub>3</sub><sup>-</sup> 10 mmol·l<sup>-1</sup>. Blood coagulation was normal. Liver functions were slightly elevated: serum glutamic oxaloacetic transaminase (sGOT) 62 U·l<sup>-1</sup>, serum glutamic pyruvic transaminase (sGPT) 123 U·l<sup>-1</sup>, respectively, (normal <40 U·l<sup>-1</sup>). Biochemistry was otherwise normal. Cystic fibrosis was excluded by a normal sweat test. An intensive search for infectious or auto-immune diseases showed no abnormalities.

The chest X-ray showed an enlarged heart shadow and a prominent pulmonary artery. There were Kerley B lines and a pronounced vascular shadowing as signs of venous congestion (fig. 1).

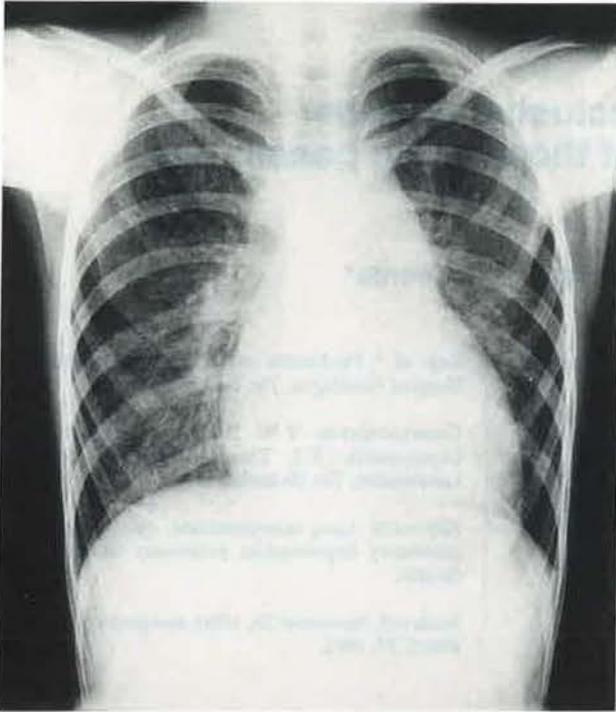


Fig. 1. - Chest X-ray of the patient.

Cardiological investigation showed increased right ventricular load: P-pulmonale and right axis deviation on electrocardiography and thickening of the right ventricle on echocardiography. The latter also showed a right-to-left atrial shunt. Cardiac catheterization could not be performed because of the poor clinical condition. Magnetic resonance imaging demonstrated normal anatomy of heart and large vessels.

Histological re-examination of the lung biopsy specimen showed intimal proliferation, formation of perivascular collagen and fibrosis with narrowing of the lumina of the veins. Thromboembolic processes, plexiform lesions or haemosiderin were not seen (fig. 2). These findings were consistent with the diagnosis of PVOD.

#### *Clinical course*

The patient had received oral corticosteroids but as no effect was noted, these were discontinued. In an attempt to decrease pulmonary vascular resistance, isoprenaline was given. This led to tachycardia (150 beats·min<sup>-1</sup>) and palpitations without clinical improvement, and was discontinued. Unilateral lung transplantation was considered, but the clinical condition of the patient deteriorated rapidly and 10 days after admission she died. Permission for autopsy was not granted.

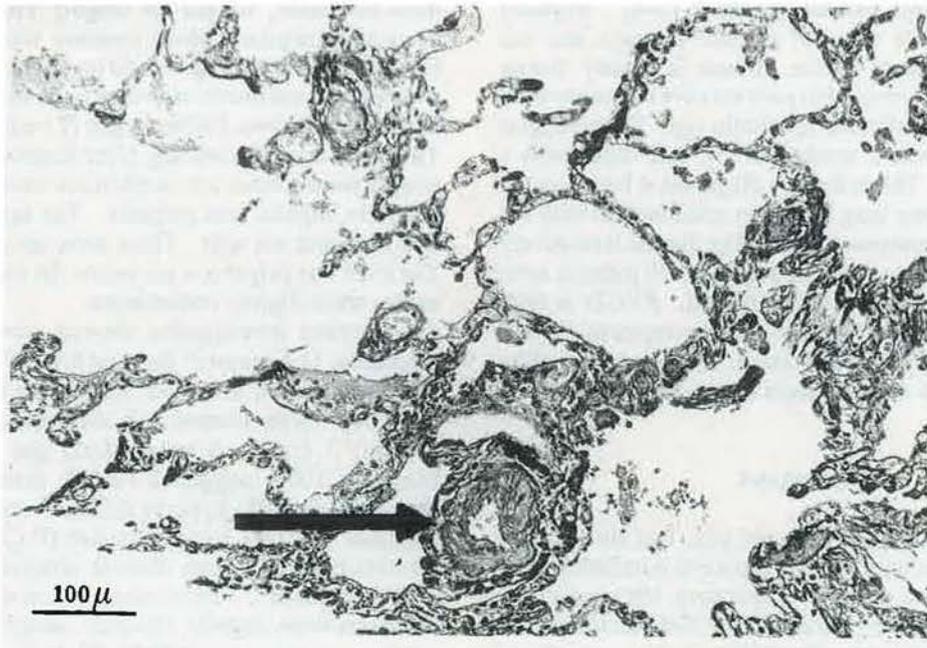


Fig. 2. - Histology of the lung biopsy magnification  $\times 140$ . Arrows: intimal proliferation and perivascular collagen. (Verhoeff's stain).

Spirometry revealed a reduced vital capacity (1.10 l, normal value for age and sex: 2.20 l, body temperature, standard pressure (BTPS)). The forced expiratory volume in one second/vital capacity (FEV<sub>1</sub>/VC) ratio was 86% (predicted value 84%).

#### **Discussion**

In this patient, the combination of the clinical signs of dyspnoea, cyanosis and cor pulmonale, with pulmonary hypertension and pulmonary venous congestion, as well

as the histological examination of the open lung biopsy led to the diagnosis of PVOD.

PVOD causes arterial desaturation by ventilation-perfusion mismatch, intracardiac and intrapulmonary shunting and diminished perfusion of the pulmonary capillaries [1]. The increased pulmonary vascular resistance leads to increased right ventricular work load and right heart failure [1]. Chest X-rays show venous congestion and right ventricular hypertrophy [11]. The latter can also be demonstrated by electro- and echocardiography.

Diseases to be considered in differential diagnosis are congenital cardiac malformation with obstruction of the left inflow tract, pulmonary vascular disorders and parenchymal diseases (table 1).

Table 1. - Differential diagnosis of pulmonary veno-occlusive disease

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**Obstruction of the left ventricular inflow tract**

Stenosis of mitral valve  
Cor triatrium  
Aortic atresia  
Anomalous pulmonary venous drainage

**Pulmonary vascular disorders**

Primary idiopathic pulmonary hypertension  
Recurrent pulmonary thrombo-embolism

**Pulmonary parenchymal diseases**

Chronic infection (viral, bacterial, parasitic)  
Cystic fibrosis  
Chronic obstructive pulmonary disease  
Hypersensitive pneumonias  
Sarcoidosis  
Pneumoconiosis  
Pulmonary haemosiderosis  
Cryptogenic fibrosing alveolitis  
Alpha-1-antitrypsin deficiency

**Others**

Sclerosing mediastinitis  
Radiation pneumonitis

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Cardiac malformations can be ruled out by physical examination, in combination with electro- and echocardiography. Sometimes a cardiac catheterization is needed to exclude cardiac disease. Magnetic resonance imaging can be a valuable alternative if the patient is unable to undergo catheterization.

Several tests are necessary to exclude other lung diseases. Infectious diseases may be demonstrated by intensive microbiological studies, including bacteriological and serological tests. Cystic fibrosis can be ruled out by sweat analysis and alpha-1-antitrypsin deficiency can be demonstrated in blood. The results of cardiac catheterization: high pulmonary arterial pressure, (almost) normal wedge pressures without anatomical

abnormalities in combination with radiological signs of pulmonary venous congestion, might suggest PVOD [8, 12].

However, an open lung biopsy is warranted for the exclusion of other parenchymal diseases and crucial for a definite diagnosis of PVOD. Microscopic examination reveals narrowing and occlusion of the vessels by acellular, fibrous tissue, often with recanalization. Venous and arterial intimal proliferation and perivascular fibrosis and elastosis are sometimes seen. Signs of interstitial or obstructive lung disorders are absent. Sometimes haemosiderosis is found [1, 9].

The cause of PVOD is unknown. A virus has been thought to be the causative agent, because some patients suffer from an influenza-like infection as did our patient [13]. Despite a thorough investigation (cultures, histology and serology), an infectious agent was never found [9].

CORRIN *et al.* [14] reported immune-complex-like deposits on electron-microscopy in a patient without clinical signs of auto-immune disease, but did not report on serological tests of auto-immunity. SANDERSON *et al.* [15] saw a patient with signs of an auto-immune disorder (arthritis, Raynaud's phenomenon, positive antibodies to smooth muscle and thyroid cytoplasm), but there are no other reports suggesting an auto-immune disease. Patients who have been exposed to chemotherapy or thoracic irradiation, are reported to have a greater risk of developing PVOD [16]. The disease has been diagnosed after bone marrow transplantation in children [17]. Inhaled irritants might also lead to the development of PVOD [1, 2].

Possibly, PVOD represents a "final common pathway" of different pathophysiological mechanisms. Some factors might disturb a delicate endothelial balance initiating local coagulation [1, 9]. Microscopy of the lungs reveals thrombus formation in the venous and arterial vasculature [7, 9]. Studies of the blood coagulation in patients with PVOD have not shown any signs of diffuse intravascular coagulation or other underlying haemostatic abnormalities.

PVOD is fatal within a few years. Some medical therapies (anticoagulants, corticosteroids, immunosuppressives, vasodilators) have been tried [3, 8, 9]. Temporary beneficial effects have occasionally been reported. Azathioprine had a positive effect in a patient with clinical and serological signs of auto-immune disease [15]. Anticoagulants might also give some temporary relief [2]. High-dose corticosteroids are reported to have some effect [17]. Recently, prolonged survival with nifedipine has been reported [10]. In our patient, neither high-dose corticosteroids nor isoprenaline, a potent vasodilator, had any effect.

Lung transplantation may offer patients a better chance. Not only might their survival be prolonged, but the quality of life might also be improved. The first follow-up studies of patients who underwent lung transplantation for fibrotic lung diseases are encouraging [18, 19]. Unilateral lung transplantation is preferable because the remaining lung has an increased vascular resistance and a diminished compliance compared with the transplanted lung. As a

result, blood flow and ventilation are directed to the latter, so that the ventilation/perfusion ratio is improved [20].

In conclusion, PVOD is a very rare disease with an extremely poor prognosis. High-dose corticosteroids, combined with nifedipine may have beneficial effects in some patients. Lung transplantation might be beneficial for patients with PVOD; this warrants a greater awareness of this disease, so that it can be diagnosed as early as possible, will make it possible to start the selection procedure for the lung transplantation in time, and to perform the transplantation at the proper moment.

### References

1. Heath D. - Pulmonary veno-occlusive disease. In: The human pulmonary circulation. P. Harris, D. Heath eds, Edinburgh, 1986, pp. 433-443.
2. Liu L, Sackler JP. - A case of pulmonary veno-occlusive disease. *Angiology*, 1972, 23, 299-304.
3. Anonymous. - Case records of the Massachusetts General Hospital (case 14-1983). *N Engl J Med*, 1983, 308, 823-834.
4. Wagenknecht C, Reinhold-Richter L, Hilgenfeld E, Haehn G. - Tödlich endende pulmonale Venenverschlusskrankheit als Ursache vegetativer Anfälle. *Kinderärztl Praxis*, 1987, 55, 259-265.
5. Voordes CG, Kuipers JRG, Elema JD. - Familial pulmonary veno-occlusive disease: a case report. *Thorax*, 1977, 32, 763-766.
6. Bjornsson J, Edwards WD. - Primary pulmonary hypertension: a histopathologic study of 80 cases. *Mayo Clin Proc*, 1985, 60, 16-25.
7. Wagenvoort CA. - Pulmonary veno-occlusive disease, entity or syndrome. *Chest*, 1976, 69, 82-86.
8. Leinonen H, Pohla-Sintonen S, Korgerus L. - Pulmonary veno-occlusive disease. *Acta Med Scand*, 1987, 221, 307-310.
9. Wagenvoort CA, Wagenvoort N, Takahashi T. - Pulmonary veno-occlusive disease: involvement of pulmonary arteries and review of the literature. *Hum Pathol*, 1985, 16, 1033-1041.
10. Salzman GA, Rosa UW. - Prolonged survival in pulmonary veno-occlusive disease treated with nifedipine. *Chest*, 1989, 95, 1154-1156.
11. Weisser K, Wyler F, Gloor F. - Pulmonary veno-occlusive disease. *Arch Dis Child*, 1967, 42, 322-326.
12. Rambihar VS, Fallen EL, Cairns JA. - Pulmonary veno-occlusive disease: antemortem diagnosis from roentgenographic and hemodynamic findings. *Can Med Assoc J*, 1979, 120, 1519-1521.
13. Wagenvoort CA, Losekoot G, Mulder E. - Pulmonary veno-occlusive disease of presumably intra-uterine origin. *Thorax*, 1971, 26, 429-434.
14. Corrin B, Spencer H, Turner-Warwick M, Beakes SJ, Hamblin JJ. - Pulmonary veno-occlusion. An immune-complex disease? *Virchow Arch*, 1974, 364, 81-86.
15. Sanderson JE, Spiro SG, Henry AT, Turner-Warwick M. - A case of pulmonary veno-occlusive disease responding to treatment with azathioprine. *Thorax*, 1977, 32, 140-148.
16. Lombard CM, Churg A, Winokur S. - Pulmonary veno-occlusive disease following therapy for malignant neoplasms. *Chest*, 1987, 92, 971-876.
17. Hackman RC, Madtes DK, Petersen FB, Clark JG. - Pulmonary veno-occlusive disease following bone marrow transplantation. *Transplantation*, 1989, 47, 989-992.
18. Higenbottam T, Otulana BA, Wallwork J. - Transplantation of the lung. *Eur Respir J*, 1990, 3, 594-605.
19. Grossman RF, Frost A, Zamel N, Patterson GA, Cooper JD, Myron PR, Dean CL, Maurer J and Toronto Lung Transplant Group. - Results of single-lung transplantation for bilateral pulmonary fibrosis. *N Engl J Med*, 1990, 322, 727-733.
20. Toronto Lung Transplant Group. - Experience with single-lung transplantation for pulmonary fibrosis. *J Am Med Assoc*, 1988, 259, 2258-2262.

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RÉSUMÉ: Nous décrivons l'observation d'une fille de 12 ans qui est décédée de maladie veino-occlusive pulmonaire. Le diagnostic reposait sur l'examen histologique d'une biopsie pulmonaire à ciel ouvert. Le diagnostic différentiel, la pathogénie et les thérapeutiques possibles, font l'objet de discussions. Quoique le traitement médical puisse parfois entraîner une amélioration temporaire, la transplantation pulmonaire pourrait offrir à ces patients de meilleures chances de survie et une amélioration de la qualité de vie.

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