Pulmonary veno-occlusive disease in pulmonary Langerhans’ cell granulomatosis


Pulmonary veno-occlusive disease in pulmonary Langerhans’ cell granulomatosis (Langerhans’ cell granulomatosis, LCG) is a rare granulomatous and fibro-inflammatory disease characterized histologically by proliferation of Langerhans’ cells with infiltration of eosinophils in the lung [1, 2]. The clinical course and prognosis of patients with pulmonary LCG is variable, ranging from spontaneous remission to respiratory failure and death due to severe lung fibrosis.

The occurrence of pulmonary hypertension in the course of pulmonary LCG is a rare event and is usually secondary to consequences of chronic hypoxia. In a few patients, pulmonary hypertension has been ascribed to arterial involvement by LCG lesions [3, 4]. In this report, an autopsy case of pulmonary LCG complicated by characteristic lesions of pulmonary veno-occlusive disease (PVOD) is presented.

Case report

The female patient’s pulmonary history began at the age of 23 yrs in 1989 with a persistent dry cough after a 1-yr smoking history (1 pack-day⁻¹). She was referred to hospital 7 months later because of mild progression of dry cough, but no haemoptysis, chest pain or apparent exertional dyspnoea was reported. Chest radiograph revealed diffuse reticulo-nodular shadows. Transbronchial biopsy (TBB) showed eosinophilic granuloma of the lung corroborated by positive immunostaining of S-100 protein on aggregated histiocytes (Langerhans’ cells), and a clinical diagnosis of pulmonary LCG was made. The patient continued smoking despite her cough symptom and against medical advice until she began to experience exertional dyspnoea and oedema in 1994. After these symptoms worsened, she was admitted to another hospital in January 1995. On admission, the chest radiograph and the chest computed tomography (CT) scan revealed increased diffuse reticulonodular and cystic shadows. She was treated with corticosteroid therapy (prednisolone 30 mg day⁻¹ and pulse treatment of methylprednisolone 1 g day⁻¹), and oxygen inhalation by nasal canula as needed, but her symptoms continued to progress. Her course was complicated by frequent episodes of right heart failure and pulmonary infections. On admission to the authors’ hospital in October 1995, she was limited to bed rest and required inhaled oxygen. Arterial blood gas examination revealed an arterial oxygen tension (P₂O₂) of 7.98 kPa (60 mmHg) while receiving oxygen therapy (10 L min⁻¹, nasal canula). Her body temperature was 36.5°C, blood pressure was 100/72 mmHg, heart rate was 120 beats min⁻¹ and respiratory rate was 28 breaths min⁻¹. On auscultation, an accentuated pulmonary component of the second heart sound and rough respiratory sounds with fine crackles were noticed. There was no finger clubbing. Blood test revealed a white blood cell count of 14,200 (cells μL⁻¹) (94% neutrophils) and 15.7 (g dL⁻¹) haemoglobin. There was mild liver dysfunction (aspartate aminotransferase 34 IU L⁻¹, alanine aminotransferase 55 IU L⁻¹, lactate dehydrogenase 1,072 IU L⁻¹) and liver congestion was suspected. Electrocardiogram revealed marked signs of right ventricular hypertrophy and right atrial overload confirmed by echocardiography. The presence of pulmonary hypertension was presumed clinically, (as a result of physical examination, electrocardiography, ultrasonic cardiography, chest radiography, and clinical course) but right heart catheterization to obtain confirmation could not be performed due to her rapidly deteriorating condition. Despite vigorous treatment for cor pulmonale and respiratory failure, she died a week later.

Autopsy findings

The significant pathological findings were confined to the heart and lungs. The heart was enlarged and mildly increased...
in weight (380 g). The right ventricle showed dilative hypertrophy with increased wall thickness (7 mm, normal <4 mm) and deviation of the septum toward the left ventricle. The wall thickness of the left ventricle was within normal limits and all cardiac valves were normal in structure. There was no evidence of either myocardial disease or congenital anomalies of the heart and large vessels. The major pulmonary arteries were dilated slightly, but were not atherosclerotic. Both lungs showed multiple and variably-sized (up to 4 cm in diameter) cystic lesions with fibrous walls. Other gross findings were congestion and oedema. Microscopically, the lung showed numerous stellate fibrous lesions of variable size which were predominantly centriacinar (centrilobular) in distribution. Cystic lesions, usually associated with these fibrous areas were also seen, ranging in size from small honeycomb lesions to large bullous areas. The stellate fibrosis and cysts were especially prominent in the upper portions of both lungs. There were no findings of active Langerhans’ cell proliferation or eosinophilic aggregation in the lung.

Pulmonary arteries near or in fibrous lesions showed medial and intimal thickening and narrowing of the lumen. Eccentric narrowing due to sclerotic changes or organized thrombi were also seen occasionally in the fibrous lesions, but were absent in normal areas. These vascular changes were interpreted as reflecting local events rather than thromboemboli. In the areas relatively normal or spared from fibrosis, medial hypertrophy of small arteries and presence of the smooth muscle in thickened media of arterioles were seen. Notably, plexiform lesions in precapillary vessels and necrotizing vascular lesions were absent. In contrast, there was a prominent narrowing or occlusion of venules due to fibrous tissue (fig. 1A). Most larger pulmonary veins showed mild thickening of the walls, but no occlusion. The veno-occlusive lesions were seen not only in areas involved by fibrosis (fig. 1B) or adjacent to the fibrosis, but normal or relatively spared areas away from the fibrous residual lesions of pulmonary LCG. In the alveoli, capillaries were dilated and frequently showed duplication including the histopathological “back-to-back” appearance. Such findings were associated with veno-occlusive lesions, some of which appeared as “nodular area of congestion”, one of the characteristic findings in PVOD [5]. Finally, dilatation of lymphatics in bronchovascular sheaths was seen. In summary, pathological findings at autopsy included both PVOD and end-staged fibrocystic lung disease due to pulmonary LCG.

Discussion

PVOD is a rare, rapidly progressive and fatal condition in which there is gradual obliteration of the pulmonary veins and venules [5]. The disease is poorly responsive to therapy, and few patients survive 2 yrs beyond the time of diagnosis. PVOD is one of the causes of "primary" pulmonary hypertension. The aetiology of PVOD is unknown; however, possible causes or associated conditions have been postulated, including [5, 6] genetic factors [6, 7], coagulopathy and thromboembolism, toxic substances and foods, viral infections [8] and auto-immune disease [9]. Moreover, some patients have developed pulmonary hypertension due to PVOD following chemotherapy for malignant disease especially leukaemia [10] and bone marrow transplantation [11]. Hence, PVOD can be considered a syndrome related to several aetiologies that may share vascular damage or lesions as a common factor [5].

Eosinophilic granuloma is a subset of histiocytosis X, which is sometimes referred to as LCG based on its patho-

Fig. 1. – A) Histological hallmarks of pulmonary veno-occlusive disease seen in this case include fibrous occlusion of pulmonary venules, prominent dilatation and duplication of capillaries in alveolar septae and hemosiderin laden macrophages in alveolar spaces (Elastica van Gieson stain; internal scale bar=100 μm). B) Pulmonary vein within an interlobular septum (*) is involved and occluded by a fibrotic lesion. An occlusive lesion in a venule (arrow) is also seen. Elastica van Gieson stain; internal scale bar=400 μm.
In conclusion, the present case demonstrates that pulmonary Langerhans’ cell granulomatosis can be associated with pulmonary hypertension due to pulmonary veno-occlusive disease. The rare patient with progressive pulmonary Langerhans’ cell granulomatosis complicated by pulmonary veno-occlusive disease faces a grave prognosis and should be considered for aggressive therapy, including lung transplantation.

References


