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CASE STUDY

Pulmonary veno-occlusive disease in pulmonary Langerhans′ cell granulomatosis

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Pulmonary veno-occlusive disease in pulmonary Langerhans′ cell granulomatosis. K. Hamada, S. Teramoto, N. Narita, E. Yamada, K. Teramoto, L. Kobzik. ©ERS Journals Ltd 2000.

ABSTRACT: This report describes unusual clinical and pathological findings in a 29-yr-old female with pulmonary Langerhans′ cell granulomatosis (LCG). During a 7-yr clinical course her condition deteriorated despite corticosteroid therapy, and she died of respiratory failure and pulmonary hypertension. At autopsy, there were widespread pulmonary veno-occlusive disease (PVOD) lesions as well as abundant advanced and healed lesions of pulmonary LCG composed of multiple cysts and stellate fibrosis.

The present case demonstrates that pulmonary Langerhans′ cell granulomatosis should be considered as a possible cause of pulmonary veno-occlusive disease.
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Pulmonary 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 (P_{a,O_2}) 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 overloading 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.

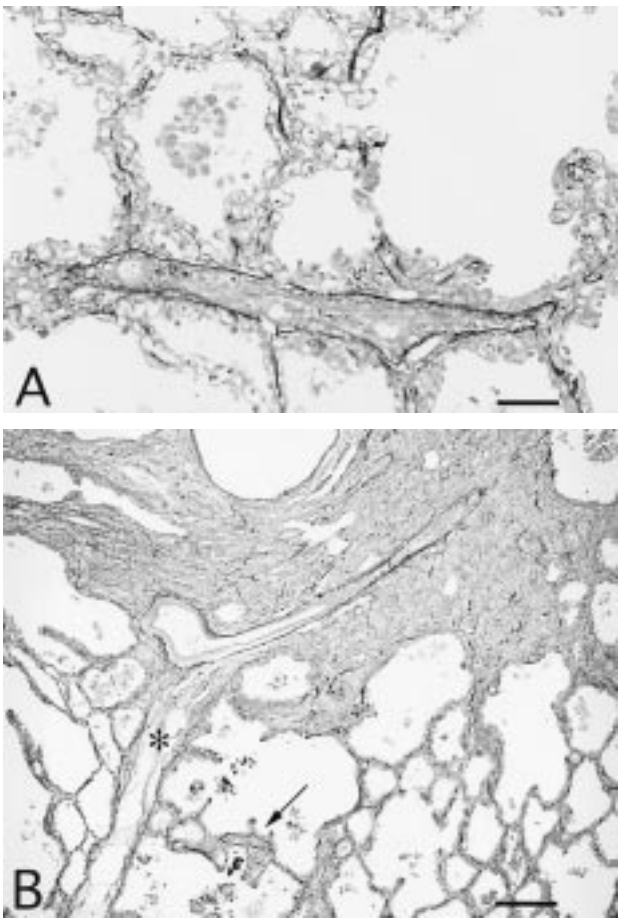

Fig. 1. – A) Histological hallmarks of pulmonary veno-occlusive disease seen in this case include fibrous occlusion of pulmonary venules, prominent dilatation and duplication of capillaries in alveolar septae and hemosiderin laden macrophages in alveolar spaces (Elastica van Gieson stain; internal scale 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.

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 pathogenic aspects. LCG is usually multifocal involving bone, skin, mucosal membrane, lymph nodes, pituitary gland, liver, and lung, either alone or in various combinations. However, when the lungs alone are affected, the condition is known as pulmonary LCG or eosinophilic granuloma of the lung. Some patients with pulmonary LCG (diagnosed clinicopathologically) have eventually shown bone involvement during their clinical course or at autopsy [1, 12]. In pulmonary LCG [1, 2], lesions are found almost entirely in a centrilobular or peribronchiolar distribution. In addition, a range of pathological stages are seen, from cellular inflammation (early) to fibrosis (late). The aetiology of pulmonary LCG is unknown; however, it occurs exclusively in smokers.

In the present case, diagnosis of pulmonary LCG was established by a transbronchial biopsy (TBB) specimen [13], which revealed granulomatous accumulation of Langerhans′ cells and confirmed by positive staining of S-100 protein immunohistochemically. Lesions of pulmonary LCG progress from nodular granulomatous lesions to cavitary or stellate shaped fibrosis lesions with perifocal emphysema. In the advanced stage of pulmonary LCG, there are many cystic lesions with fibrotic walls or "healed" fibrous stellate lesions and perifocal emphysema surrounded by fibrous

walls. In some cases where radiological evaluation shows apparent remission, this corresponds pathologically to small and scattered lesions that have undergone to fibrosis. In the present case, there were many cystic lesions with fibrous walls and scattered stellate fibrosis of the lung at autopsy. Neither active granulomatous lesions nor accumulation of eosinophils was seen. These findings indicate that the lesions of pulmonary LCG had progressed to the late fibrous stage in the patient′s 7 yr clinical course after diagnosis by TBB.

Symptoms of patients with pulmonary LCG are usually rather mild despite alarming radiological abnormalities. The clinical course and prognosis is variable, and ranges from spontaneous remission to progressive respiratory failure and death. Some patients show radiological resolution upon cessation of smoking. From a recent study [12], the probability of survival of patients with pulmonary LCG is >70% 10 yrs after diagnosis. The role of medical therapy is controversial. In the present case, high dose methyprednisolone (pulse therapy) and prednisolone were used after the patient′s symptoms, which were compatible with pulmonary hypertension, had increased. While this therapy was not ultimately effective, it is a possible factor in the absence of active LCG lesions at autopsy.

There have been some reports of pulmonary hypertension in patients with pulmonary LCG [3, 4, 14, 15]. While chronic hypoxia due to diffuse fibrosing lung diseases can cause secondary pulmonary hypertension, pulmonary LCG can also directly involve blood vessels within lesions [1, 2]. Histologically, various degrees of arterial and arteriolar changes have been correlated to the presence of precapillary pulmonary hypertension [1, 3, 4] including striking examples reported by FRIEDMAN *et al.* [16] and HARARI *et al.* [14]. The former found inflammatory cell infiltration of vessel walls (which was diagnosed as vasculitis, although no necrotizing component was seen). In another interesting report, HARARI *et al.* [14] found obstruction of vascular lumena by Langerhans′ cells. It is possible (although clearly speculative) that a similar process led to the veno-occlusive disease in this case. TRAVIS *et al.* [17] also described vascular mural inflammation in both arteries and veins in 70% of biopsies in his review of pulmonary LCG. BASSET *et al.* [1] described venous involvement within lesions and KAWABATA *et al.* [18] referred to obstructive lesions of veins and venules in an autopsy case. In the present case, there were veno-occlusive lesions distributed widely in the lung with hypertensive changes in the precapillary vessels. Veno-occlusive lesions were located not only close to the fibrous lesions of pulmonary LCG, but also areas removed from and spared such fibrosis. The surrounding alveolar area showed severe congestive capillary changes. As described above, because no active granulomatous lesions were seen at autopsy, the pathogenesis of PVOD could not be further elucidated in the present case. It is noteworthy that BENYOUNES *et al.* [3] reported a case of pulmonary hypertension associated with arterial involvement by LCG. Although corticosteroid therapy was effective in that study, it was ineffective in the present case. Corticosteroids can themselves increase risk of thromboembolism and potentially contribute to pulmonary vascular disease. However, it is unlikely that this was a factor in this patient′s history because her clinical deterioration occurred before such therapy and there was no definitive evidence of thromboembolism pathologically.

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.

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