Spherocytosis and pulmonary hypertension coincidental occurrence or causal relationship?

D. Verresen, W. De Backer, J. Van Meerbeeck, I. Neetens, E. Van Marck, P. Vermeire

ABSTRACT: A report is given on a 59 yr old man with hereditary spherocytosis and progressive shortness of breath on exertion, due to severe pulmonary hypertension and cor pulmonale. An open lung biopsy was performed in order to exclude all known aetologies of secondary pulmonary hypertension. Pathological examination revealed in situ thrombosis and asymmetric fibromuscular hyperplasia of small- and medium-sized pulmonary arteries. Both primary pulmonary hypertension and hereditary spherocytosis have a low incidence in the general population and their simultaneous occurrence has not been reported previously; the possibility that this was due to a causal relationship and not to coincidence cannot be ruled out, in view of some similarities with pulmonary hypertension complicating sickle cell anaemia.

Pulmonary hypertension may be either primary or secondary. The diagnosis of primary pulmonary hypertension (PPH) requires the exclusion of any of the several known causes of secondary hypertension [1-9]. We report the occurrence of pulmonary hypertension in a patient with hereditary spherocytosis and extramedullary haematopoietic tumours.

Case report

A Caucasian male, housekeeper aged 59 yrs, had been experiencing progressive dyspnoea on exertion (New York Heart Association grade II), for four months without wheezing or orthopnoea. He also had had a mild chronic cough with sputum production, despite stopping a smoking habit of 20 pack-years one year ago. An emergency hospitalization because of acute abdominal pain at the age of 39 yrs had led to the diagnosis of cholelithiasis and a nonspecific "blood abnormality". His mother had died at the age of 30 yrs during a gall-bladder operation and a niece had recently undergone cholecystectomy and splenectomy for a "haemolytic disease".

On physical examination at the time of referral the only notable finding was a palpable spleen. A chest radiograph demonstrated bilateral enlarged vascular hili and decreased peripheral vascular lung markings. Computerized tomographic (CT)-scan of the thorax did not show hyperinflation, suggestive of emphysema; however, it showed tumoural opacities in both paravertebral areas (fig. 1). Routine pulmonary function data were compatible with a mild obstructive pattern (vital capacity (VC) 79%, residual volume (RV) 166%, total lung capacity (TLC) 104%, forced expiratory volume in one second (FEV1) 69% of predicted and a FEV1/VC ratio of 0.62) with a marked decrease in diffusing capacity (Dco 46% of predicted). Arterial blood gas measurement showed hypoxaemia despite mild hyperventilation (arterial oxygen tension \(P_{\text{aO}_2}\) 8.5 kPa, arterial carbon dioxide tension \(P_{\text{aCO}_2}\) 4.4 kPa, pH 7.46, plasma bicarbonate 22.8 mmol.L\(^{-1}\)).

Fig. 1. – Computerized tomographic (CT)-scan showing an inhomogenous tumoural opacity in the left paravertebral area of the thorax. A similar opacity was present more cranially/caudally on the right side.
The electrocardiogram indicated right axis and right ventricular hypertrophy and these signs of cor pulmonale were confirmed by echocardiography. A lung perfusion scan showed a markedly nonhomogeneous perfusion but no typical signs of pulmonary embolism. Exercising capacity during an ergometer test was limited to 50 W; at this level maximal heart frequency was 109 beats·min⁻¹ (67% of predicted) and maximal \(\text{O}_2\) uptake (\(\text{VO}_2\) max) 11.4 ml·min⁻¹·kg⁻¹ (34% of normal value), whereas \(\text{O}_2\) saturation measured by ear oximeter had fallen from 98 to 91%.

Routine laboratory testing yielded a haemoglobin concentration of 12.7 g·dl⁻¹ and a white blood count of 8,000·mm⁻³ with normal differentiation. In addition there was marked reticulocytosis (15%) and spherocytosis (19%), with severely diminished osmotic resistance, low haptoglobin concentration, negative direct Coombs reaction and normal haemoglobin electrophoresis. Total and direct bilirubin concentrations were 2.5 and 1.04 mg·dl⁻¹, respectively.

Abdominal echography showed cholelithiasis, splenomegaly and a wide inferior vena cava. Right heart catheterisation confirmed the presence of severe pulmonary hypertension, with systolic, diastolic and mean pulmonary artery pressures of 79, 19 and 39 mmHg, respectively; mean capillary wedge pressure was 12 mmHg. Pulmonary angiography showed severely diminished peripheral vascular filling without signs of pulmonary embolism; on phlebography of the lower extremities no signs of thrombosis were detected.

A left thoracotomy was requested, both for biopsy of the lung parenchyma in order to exclude known causes of pulmonary hypertension, and for biopsy of a para­vertebral tumour. The lingula biopsy showed an trilinear hyperplasia and relative predominance of the erythrocyte line. Like sickle cells, such erythrocytes are no longer deforming adequately in the blood stream, causing increased blood viscosity and intrapulmonary red cell sequestration, and they lead to vascular stasis and even complete blockage of the microvasculature. Pulmonary hypertension and cor pulmonale mostly develop after multiple episodes of non-embolic pulmonary infarcts. Fat or necrotic bone marrow emboli originating from extramedullary haematopoietic sites have also been incriminated in this process [13-16].

One could wonder whether such \textit{in situ} pulmonary vascular occlusion could similarly have been caused by the defect in red blood cell membrane formation present in hereditary spherocytosis. This defect has been attributed to a deficiency in spectrin, the largest and most abundant structural protein of the red cell membrane skeleton, providing the flexibility and durability necessary for the erythrocyte to resist the turbulence inside the circulation. Spectrin deficiency in the membrane skeleton leads to a gradual loss of red cell surface area, causing erythrocytes to become spherical instead of remaining biconcave discs. Like sickle cells, such erythrocytes are no longer deforming adequately in the

**Discussion**

This patient presented with the rare combination of hereditary spherocytosis and marked pulmonary hypertension, the latter progressing rapidly to death. Spherocytosis was causing characteristic features of a chronic haemolytic syndrome with extramedullary haematopoiesis in pseudotumours located in both thoracic paravertebral areas. He had cholelithiasis which is another common finding in such patients [10-12]. His pulmonary hypertension is to be considered as primary, since known causes of secondary pulmonary hypertension were excluded by open lung biopsy findings; in particular there was no indication of repeated pulmonary embolism and histological findings were compatible with this diagnosis [1-9].

We were unable to trace any previous report of the combined presence of both disease entities in the literature. By contrast, severe pulmonary vascular disease has been reported in patients with sickle cell haemoglobinopathies SS, SC and SB thalassaemia. In such cases autopsy specimens have revealed asymmetric intimal thickening and widespread occlusions of small- and medium-sized arteries with old, organized recanalized thrombi. In these haemoglobinopathies red cells are more rigid and nondeformable; they have also been reported to bind to endothelial cells. Both features cause increased blood viscosity and intrapulmonary red cell sequestration, and they lead to vascular stasis and even complete blockage of the microvasculature. Pulmonary hypertension and cor pulmonale mostly develop after multiple episodes of non-embolic pulmonary infarcts. Fat or necrotic bone marrow emboli originating from extramedullary haematopoietic sites have also been incriminated in this process [13-16].
microcirculation [12]. One would thus envisage that this disturbance also leads to in situ microvascular thrombosis, extensive vascular narrowing and occlusions, resulting in pulmonary hypertension and cor pulmonale.

We were unable to detect in our patient any feature that could have rendered him more prone to developing pulmonary hypertension than other patients with hereditary spherocytosis. Should one, thus, regard this combination as a coincidental occurrence or as resulting from an unusual causal relationship? Both non-embolic pulmonary hypertension and hereditary spherocytosis are relatively rare conditions in the general population. This would favour a causal relationship, and such premise is strengthened by similarities with sickle haemoglobinopathies. However, a hypothesis that hereditary spherocytosis be regarded as another cause of secondary pulmonary hypertension would need support from further observations.

References

