Prof. Ivo Šteiner, MD, PhD, Editor

CASE 1-2009: A 65-YEAR-OLD WOMAN WITH THREE MONTHS' HISTORY OF PROGRESSIVE DYSPNEA AND RECURRENT EPISODES OF COLLAPSE

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Clinical data

A 65-year old woman was admitted for sudden collapse during walking. First she felt dyspnea and presternal chest pain without irradiation, and then she collapsed, losing consciousness for 30–60 seconds without incontinence or muscle cramps.

The patient had a 17-year history of angina pectoris (but coronary catheterization did not reveal any coronary stenosis) and an 8-year history of arterial hypertension. She had one episode of unprovoked deep vein thrombosis 27 years ago, carpal tunnel operation and cholecystectomy 18 years ago, and appendectomy 14 years ago. The patient was married with two children. Before retirement she worked as a dressmaker. She did never smoke or drink alcohol and had no known allergies. Her medication included perindopril, citalopram, omeprazol and nimesulid. During previous three months she had several episodes of precollapse, and of chest, epigastric and back pain. Progressive dyspnea has limited her walking during the last three weeks.

On admission the patient was oriented to person and place. She had slightly slower psychomotor activity and normal neurological reflexes. Her blood pressure was 176/110 mmHg, the pulse was well palpable at 102 beats per minute, jugular venous pressure was elevated. She had moderate respiratory distress; the respiratory rate was 40 per minute, and the breath sounds were diminished over the inferior field of the right lung. Percussion over this place was dull. The liver was palpable 5 cm below the right costal margin. The extremities were cold and cyanotic, but pulses on the extremities were present and equal. On electrocardiogram, there was sinus tachycardia with heart rate 102 per min, right axis deviation (+150 °), small r wave from V1 to V6, and non specific T wave changes (Fig. 1). The right axis deviation and small r wave from V4 to V6 were new changes as they were not seen on a record from 6 months ago (Fig. 2). On chest radiogram, there was a large right and small left pleural effusion. Intravenous catheter was placed in the right subclavian vein and central venous pressure was measured (+25 cm H_2O). Perfusion lung scan showed bilateral subsegmental perfusion defect. Laboratory findings are summarized in Tab. 1. The clinical signs of right ventricular failure, the result of perfusion scan and elevation of D-dimer suggested pulmonary embolism. Therefore, the treatment with low molecular weight heparin (enoxaparin 0.6 ml s.c. b.i.d.) was started immediately. Also, acetylsali-

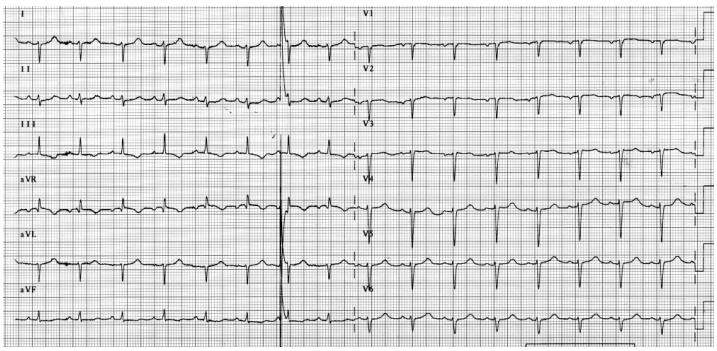

Fig. 1: Electrocardiogram on admission.

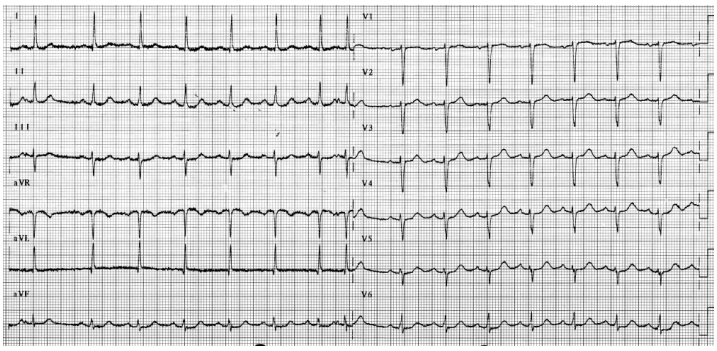

Fig. 2: Electrocardiogram 6 months ago.

Tab. 1: Results of laboratory tests on admission.

Variable	Unit	Value	Ref. Range
Hemoglobin	g/L	162	120–162
White cell count	x 10^{12}/L	14.77	3.9–9.4
Differential count	fractions		
– segmented neutrophils		0.84	0.48–0.7
– band forms		0.01	0.01–0.02
– lymphocytes		0.07	0.23–0.45
– monocytes		0.08	0.02–0.08
Platelets	x 10^9/L	114	150–396
D dimer	mg/L	5.88	0–0.5
Prothrombin time	s	27.1	14.9
Sodium	mmol/L	141	135–148
Potassium	mmol/L	4.2	3.5–5.1
Urea	mmol/L	18.4	2.5–8.3
Creatinine	μmol/L	165	50–95
Glucose	mmol/L	10	3.3–5.6
Troponin T	μ/L	0.067	0–0.03
Creatine kinase	μkat/L	2.33	0.8–2.12
– MB isoenzyme	μkat/L	0.92	0 – 0.5
Total bilirubin	μmol/L	87	3–17
– direct bilirubin	μmol/L	50	0–6
AST	μkat/L	8.58 /	0.18–0.55
ALT	μkat/L	8.78	0.18–0.52
Total protein	g/L	63.4	35–52
CRP	mg/L	29	0–5
Lactate (arterial)	mmol/L	5.83	0.6–2.4
pH (arterial)		7.419	7.36–7.44
pCO_2 (arterial)	kPa	3.4	4.8–5.9
pO_2 (arterial)	kPa	10.0	9.9–14.0
Bicarbonate (arterial)	mmol/L	19.4	22–26
Base excess (arterial)	mmol/L	-6.1	-2.5–2.5
O_2 saturation (arterial)	%	93.5	

cylic acid and continual infusions of furosemide and glycerol trinitrate were administered.

However, as the diagnosis of thromboembolic disease was not clear, CT angiography was performed. It failed to reveal any massive or segmental pulmonary embolism. Chest drain was inserted into the right pleural cavity and approximately 1500 ml of fluid was drained; laboratory examination documented transudate. Transthoracal echocardiography showed normal left ventricular contractions with ejection fraction 70 %, right atrial and ventricular dilatation, tricuspidal regurgitation and pulmonary hypertension (estimated systolic pulmonary artery pressure 80 mmHg). Shortly after transesophageal echocardiography (not revealing any other pathology) the patient presented with hyposaturation, hypotension and sinus bradycardia. Cardiopulmonary resuscitation was instituted, with restoration of sinus rhythm for a limited time. Thereafter pulseless electric activity appeared and resuscitation efforts failed. The patient was pronounced dead 31 hours after admission to our department. Because of rapid clinical deterioration and not fully explained severe pulmonary hypertension, autopsy was asked.

Clinical diagnosis: Primary pulmonary hypertension.

Pathological findings

Grossly, the autopsy findings were rather non specific – congestion in splanchnicum, right ventricular myocardial hypertrophy and mild hydrothorax bilaterally. There were no signs of thromboembolism and there was no pulmonary fibrosis. Atherosclerotic changes were minimal. Other findings were appropriate to the age of the patient.

Microscopically, the lung arteries and particularly arterioles showed marked hypertensive changes. The media was thickened and the intima showed concentric fibrosis (Fig. 3). There were multiple plexiform or angiomatoid lesions in smaller arterioles (Fig. 4). There was no fibrosis in the pulmonary parenchyma, only congestion (sometimes with siderophages) and scarce acute small thrombi or thromboemboli in peripheral arteries. There were no postembolisation changes and the capillary and venous system appeared normal. These changes are considered as signs of primary pulmonary hypertension.

In the bone marrow there were focal lymphoid infiltrates; the lymphocytes were small and immunohistochemically positive for CD 20 and bcl2. In a mediastinal lymph node there was mild expression of CD 23 outside the germinal centers. We conclude, the patient had a small cell lymphoma, probably of the CLL/SLL subtype.

In the heart, in addition to marked right ventricular myocardial hypertrophy, there were changes also in the left ventricle – hypertrophy of the cardiomyocytes and irregular architecture with branching. This finding ("disarray") is encountered in hypertrophic cardiomyopathy, however, our case lacked the gross features of this entity.

In the ascending aortic wall, there were foci of medial smooth muscle necrosis (medionecrosis).

Pathological diagnosis: Primary pulmonary hypertension.

Discussion

The question is, what was the cause of the patient's severe pulmonary hypertension (PH) that resulted in acute right ventricular failure. There may be primary and secondary clinical entities associated with pulmonary hypertension. Primary (arterial) PH includes idiopathic and familiar forms. Most familiar and 20 % of idiopathic cases of primary PH have mutation in the gene coding the type 2 bone morphogenetic protein receptor (BMPR 2), a member of the transforming growth factor (TGF)-beta superfamily. This abnormality may stimulate serotonin production and endothelial and smooth muscle proliferation. In patients with primary PH, there is significantly enhanced activity of thromboxane and endothelin-1 (both vasoconstrictors) and reduced activity of prostacyclin and nitric oxide (both vasodilatators). Injuries of the endothelium may activate coagulation. Precapillary hypertension, plexogenic arteriopathy and significant improvement with prostacyclin analogues are features typical of arterial PH.

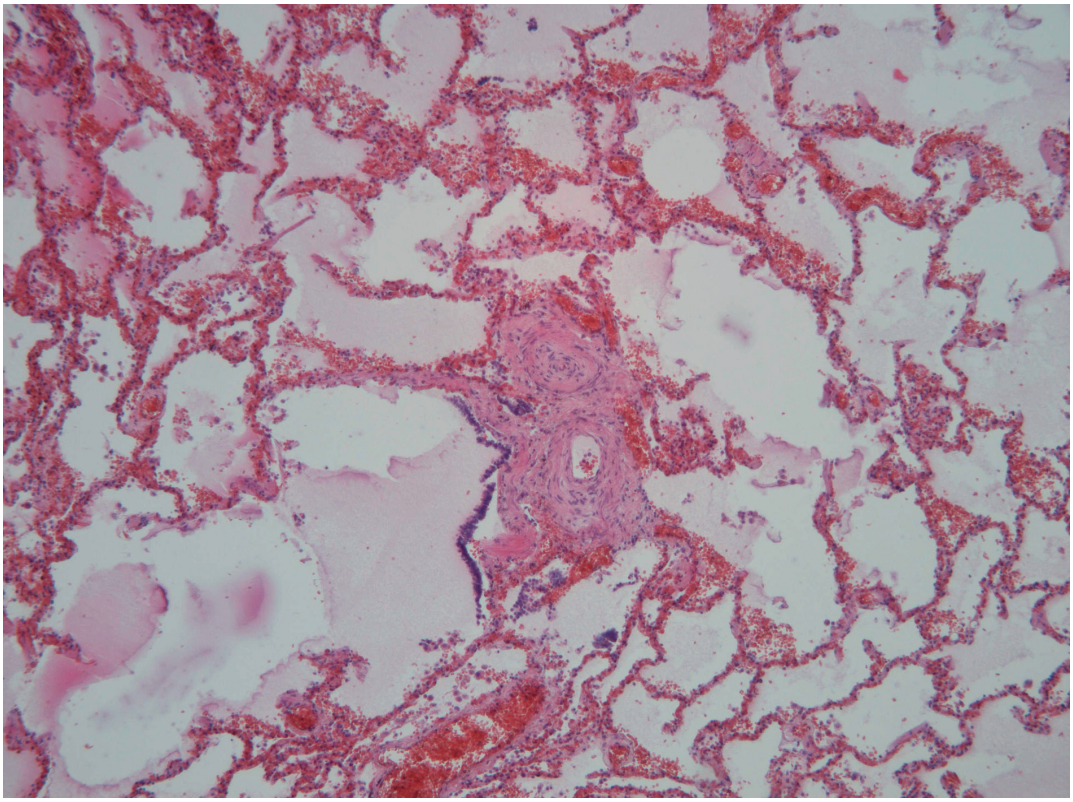

Fig. 3: Small arteries with markedly thickened media and concentric lamellar fibrosis of intima.

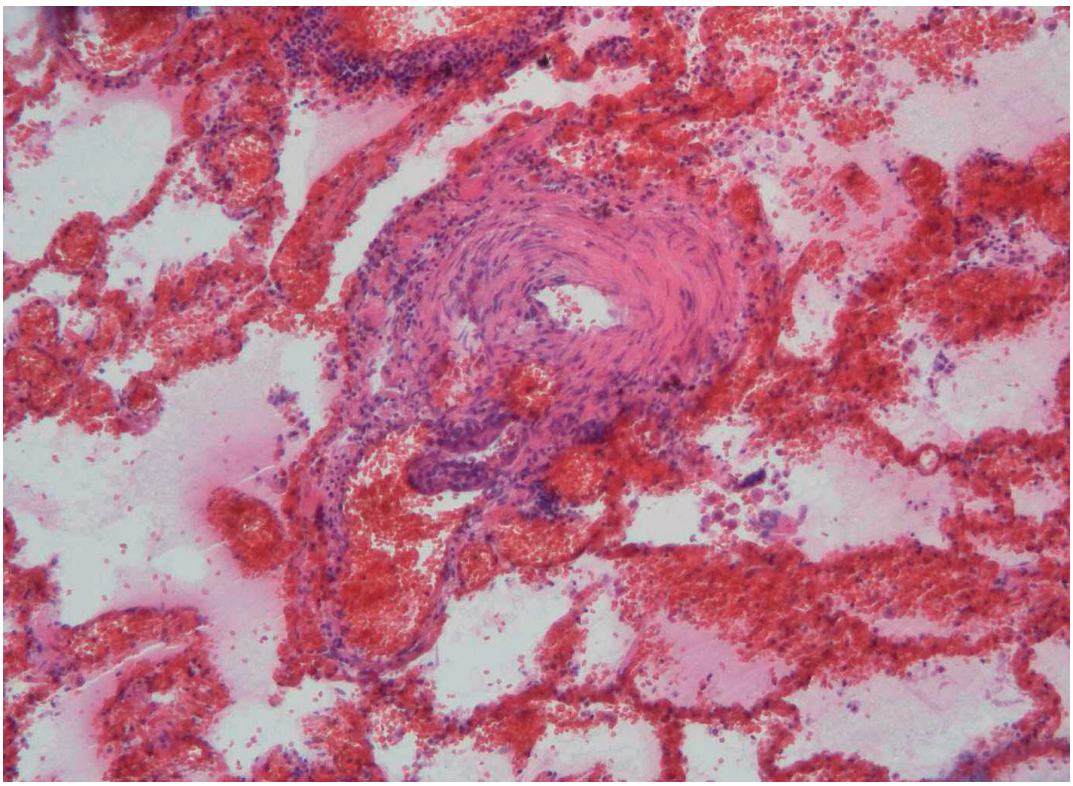

Fig. 4: Small artery with a plexiform lesion.

The causes of secondary PH include left ventricular dysfunction, chronic obstructive pulmonary disease, chronic hypoxemia of any cause, intracardiac left-to-right shunts, pulmonary thromboembolic disease, systemic vasculitis, and some other rare causes.

The histopathological diagnosis of pulmonary hypertension is based on studies on patients with congenital heart disease. The six-grade grading system by Heath and Edwards (2) (Table 2) is also applicable in adult patients. The first three grades may be found in secondary hypertension. Grades I and II are often seen in pulmonary diseases (emphysema, interstitial lung diseases), grade III in severe pulmonary or heart diseases, in chronic thromboembolism (together with other post-embolism changes), or in venoocclusive disease (together with changes in venous structure in pulmonary septa). Grades IV and V are typical of primary pulmonary hypertension/plexiform arteriopathy. Grade VI is only seen in children with congenital heart malformations. In recent modifications of this grading system, the grades IV, V and VI are sometimes summarized into one grade (IV–VI). The diagnosis and grade of pulmonary hypertension may be established by bioptic examination of a pulmonary excision (1, 2, 4).

Tab. 2: Classification of pulmonary hypertension by Heath & Edwards (2).

Grade I	medial hypertrophy of pulmonary arteries and muscularization of arterioles
Grade II	intimal proliferation in arteries
Grade III	intimal concentric laminar fibrosis becomes prominent in muscular arteries
Grade IV	dilation of small arteries occurs with development of plexiform lesions
Grade V	plexiform and angiomatoid lesions become prominent; hemosiderin deposition present
Grade VI	necrotising arteritis

Although we have found in the left ventricle myocardial lesions seen in hypertrophic cardiomyopathy, both the clinical and gross pathological findings do not confirm this diagnosis, therefore excluding secondary pulmonary hypertension. In addition, the grade IV and V changes seen on the pulmonary arteries are practically diagnostic for primary pulmonary hypertension. It is therefore possible to speculate that the described changes in the pulmonary arteries, the myocardium and the aortic wall may have a common etiology – an inborn abnormality of the connective tissues.

The cause of PH in our case was unknown. Although cardiac catheterization and bioptic examination were not performed due to lack of time, no clinical signs associated with secondary PH were documented. The microscopic findings supported the clinical diagnosis of primary PH.

Untreated patients with primary PH have a median survival of 2.5 years. The mode of death is usually a sudden death in the context of right ventricular failure, as in our patient. In the treatment of primary PH, calcium channel blockers, prostacyclin analogues, bosentan (an endothelin receptor antagonist), and sildenafil (a phosphodiesterase-5 inhibitor) are used. Lung transplantation is indicated in selected cases only.

Message from the Editor (Prof. Šteiner)

Pulmonary hypertension (PH) is clinically defined as a pulmonary arterial pressure greater than 25 mmHg at rest or greater than 30 mmHg during exercise.

PH is most often **secondary** to chronic obstructive or interstitial lung disease, to recurrent pulmonary emboli, or to antecedent heart disease, e.g. mitral stenosis, or congenital left-to-right shunts.

Uncommonly, PH exists even though all known causes of increased pulmonary pressure can be excluded; this is referred to as **primary** or **idiopathic** PH. Of these, the vast majority of cases are sporadic and only 6 % have the familial form with an autosomal dominant mode of inheritance.

Due to inadequate time, the case presented has not been fully clinically investigated. However, both clinical and pathological examinations did not document any cause of secondary hypertension in the 65-year-old woman. The histological finding of the complex (plexiform/angiomatoid) pulmonary artery lesions appears as a strong support for the diagnosis of primary/idiopathic pulmonary hypertension.

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