IDIOPATHIC PULMONARY HYPERTENSION, DIAGNOSED IN THE FORENSIC EXAMINATION OF A 3-YEAR OLD DIED FROM UNRELATED CAUSE

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ABSTRACT

Idiopathic (historically known as primary) pulmonary hypertension (IPH) is defined by increasing the mean arterial pulmonary pressure to greater than 25 mm Hg at rest in the absence of an identifiable etiology and familial history. We present a case of a 3-year-old male child who developed an acute viral infection of the upper respiratory tract. There were no medical data about inherited diseases in the family. Symptoms included high temperature (up to 39.8ºC), vomiting and diarrhea and were treated with anti-inflammatory drugs. The child died on the way to the hospital. During the forensic medical internal examination were established catarrhal bronchitis, catarrhal enterocolitis, and reactive hyperplasia of peribronchial and mesenterial lymph nodes. There were mild hypertrophy and dilatation of the right heart ventricle without any congenital heart defects. H&E, Elasica-Van Gieson and Azan stained slides from the lungs revealed the following findings: 1. "Constrictive" lesions characteristic for the early phase of pulmonary hypertension - small pulmonary arteries with severe medial hypertrophy and intimal proliferation with periadvential fibrosis; 2. Specific for the late phase "complex" lesions - angiomatoid lesions with formation of vein-like branches of the pulmonary arteries. There were also old and recent thrombi, diffuse atelectases and compensatory emphysema. Wide spread hemosiderosis was not observed. Based on the described gross and histological changes, the cause of death was atributted to acute viral infection that occurred on the background of clinically unmanifested idiopathic pulmonary hypertension.

Key words: idiopathic (primary) pulmonary hypertension, sudden death, histology.

INTRODUCTION

Pulmonary hypertension (PH) refers to a group of diseases characterized by an elevation in mean arterial pulmonary pressure to greater than 25 mm Hg at rest as assessed by right heart catheterization. Idiopathic (historically known as primary) pulmonary hypertension (IPH) is defined by increasing the pressure in the absence of an identifiable etiology (e.g. congenital heart disease, lung diseases, chronic pulmonary thromboembolism, or other rare diseases). IPH affects mostly young people. The lowest estimate of the prevalence of IPH is 5,9 cases/million adult population (5, 9).

The pulmonary blood vessels have a limited repertoire of responses to injury. Under different types of injuries, pulmonary vessels respond with wall remodeling that include changes in all three layers – intima, media, and adventitia – and that are the consequence of cellular hypertrophy, hyperplasia, migration, and apoptosis, associated with matrix deposition and degradation (11). The balance between these cellular and molecular events will result in morphological lesions of a certain

severity and extension. Regardless of etiology, the final common pathway of PH is right heart failure and death. IPH may cause sudden death as an initial manifestation of the disease in individuals of all ages, including a few pediatric cases reported with sudden death (1, 2, 3, 13). The challenge for the pathologists remains the identification of histologic patterns of vascular lesions which identify subset of patients with IPH.

CASE PRESENTATION

We present a case of a 3-year-old male child who developed an acute viral infection of the upper respiratory tract. There were no medical data about inherited diseases in the family. Symptoms included high temperature (up to 39.8ºC), vomiting and diarrhea and were treated with anti-inflammatory drugs. The child died on the way to the hospital. Forensic medical autopsy of the cadaver was performed. There were no significant findings on the external examination. During the internal examination were established catarrhal bronchitis, catarrhal enterocolitis, and reactive hyperplasia of peribronchial and mesenterial lymph nodes. There were mild hypertrophy and dilatation of the right heart ventricle without any congenital heart defects. For histological examination samples from all of internal organs were submitted. H&E, Elasica-Van Gieson and Azan stained slides from the lungs revealed the following findings: 1. "Constrictive" lesions characteristic for the early phase of pulmonary hypertension - small pulmonary arteries with severe medial hypertrophy and intimal proliferation with periadvential fibrosis (Fig. 1A, B, C); 2. Specific for the late phase "complex" lesions - angiomatoid lesions with formation of vein-like branches of the pulmonary arteries (Fig. 1D, E, F). There were also old and recent thrombi, diffuse atelectases and compensatory emphysema. Wide spread hemosiderosis was not observed. Based on the described gross and histological changes, the cause of death was atributted to acute viral infection that occurred on the background of clinically unmanifested idiopathic pulmonary hypertension.

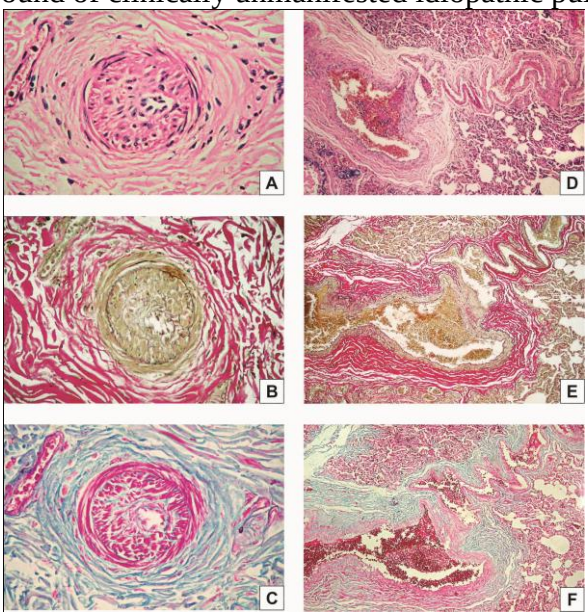

Fig. 1. A, B, C: small pulmonary arteries with severe medial hypertrophy and intimal proliferation with periadvential fibrosis; **D, E, F**: vein-like branches of the pulmonary artery. **A, D** – Hematoxylin&Eosin; **B, E** – Elastica-van Gieson; **C, F** – Azan.

DISCUSSION

PH is a heterogeneous group of diseases with different etiologies and pathophysiological mechanism. The current clinical classification system for PH consists of six categories, based on the similarities in pathophysiologic mechanisms, clinical presentation, and therapeutic approaches (12).

The first category includes idiopathic and heritable forms, as well as PH associated with other risk factors or diseases, such as drugs and toxins, connective tissue diseases, congenital heart disease, HIV infection and others. IPH corresponds to sporadic disease without any familial history or known triggering factor. The old term familial has been replaced by heritable because specific gene mutations has been identified in sporadic cases with no family history. Heritable forms of PH include clinically sporadic idiopathic cases with germline mutations (mainly of the *BMPR2* as well as the *ALK1* or the *endoglin* gene) and clinical familial cases with or without identified germline mutations (6, 7).

Pathological lesions in the first clinical group of PH affect the distal pulmonary arteries (< 500 μm of diameter) in particular. They are characterized by medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with moderate perivascular inflammatory infiltrates, complex lesions (plexiform, dilated lesions) and thrombotic lesions (10, 14). Pulmonary veins are classically unaffected. Vasoconstriction, vascular cell proliferation and thrombosis are thought to be the central players in the pathogenesis of these lesions, probably with a key initiator role for damaged or activated endothelial cells. Indirect evidence derives from altered plasma levels of key mediators of these processes, such as increased thromboxane A2, endothelin-1 and serotonin, and decreased prostacyclin, nitric oxide and vasoactive intestinal peptide (4).

For many years plexogenic pulmonary arteriopathy (PPA) was considered the most specific for the first group of PH histologic complex of changes. PPA has an early reversible and a late, irreversible and progressive phase (8). The early phase is histologically non-specific, with pulmonary arterial medial hypertrophy and mild intimal thickening representing the sole abnormalities. Later, more distinctive and – ultimately – pathognomonic plexiform lesions arise. The plexiform lesion is a small arterial lesion (generally <300 μm) situated just distal to an arterial branching site. It consists of a plexus of slit-like channels lined by small, flat endothelial cells and subjacent myofibroblasts, enclosed within, or in continuity with, a greatly dilated segment of the affected small artery. Some thrombus fragments are common within the abnormal vascular spaces. Traces of fibrinoid necrosis of the vessel wall may be discernible, mostly immediately proximal to the plexus. Distal to the plexus, there is commonly a marked dilatation of the affected arterial branch, and similar dilatation may occur without the formation of the plexus that characterizes the plexiform lesion. The latter situation results in so-called vein-like branches; clusters of these have been dubbed angiomatoid lesions. In severe, advanced PPA, arteritis is occasionally detected.

PH is a progressive disease that leads to cor pulmonale and death. Most patients experience gradually worsening symptoms of dyspnea, syncope, and congestive heart failure, but a small number die suddenly and unexpectedly. Since PH may go undiagnosed in life, it is important for the forensic pathologist to be aware of the condition and associated pathologic features. On autopsy, right ventricular hypertrophy and dilatation will likely be the first sign of PH. Careful histologic examination is necessary to confirm the diagnosis, and lung tissue must be handled appropriately. Sampling should include blocks from each lobe to ensure that adequate numbers of blood vessels are obtained, since characteristic lesions are irregularly distributed throughout the lung. Sections should be stained with Hematoxilin&Eosin, as well as special stains such as Masson, elastica-van Gieson, and Perls' iron, to assist in the evaluation of vascular pathology.

IN SUMMARY, we present a rare case of occult IPH in a 3-year-old child, revealed after unexpected sudden death occurred due to added viral infection. The diagnosis of IPH, particularly in forensic cases, requires that the pathologist be especially aware of the possibility and that a careful evaluation of multiple sections of lung be performed. Determination of the histopathologic type also is important because some forms of the disease may be familial and may be treatable in other family members if they are detected early.

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