

Case Report

Clinical and Morphological Features of Primary Pulmonary Hypertension: The Analysis of Two Cases from Practice

Iryna Viktorivna Sorokina¹, Igor Volodymyrovych Kuznetsov², Iryna Vasylivna Borzenkova³, Yuliia Igorivna Maslova¹, Mykhailo Sergiyovych Myroshnychenko^{1,*}, Galyna Mykolayivna Saldan⁴, Vitaliy Leonidovych Levinskiy³, Olexiy Oleksandrovych Lyubchenko¹

¹Department of Pathological Anatomy, Kharkiv National Medical University, Kharkiv, Ukraine

²Department of Cardiology, The Public Health Care Institution «The Regional Clinical Hospital – The Center of Emergency Medical Care and Disaster Medicine», Kharkiv, Ukraine

³Department of Pathological Anatomy, The Public Health Care Institution «The Regional Clinical Hospital – The Center of Emergency Medical Care and Disaster Medicine», Kharkiv, Ukraine

⁴The Public Health Care Institution «The Center of Emergency Medical Care and Disaster Medicine», Kharkiv, Ukraine

Email address:

mmyroshnychenko@ukr.net (M. S. Myroshnychenko)

*Corresponding author

To cite this article:

Iryna Viktorivna Sorokina, Igor Volodymyrovych Kuznetsov, Iryna Vasylivna Borzenkova, Yuliia Igorivna Maslova, Mykhailo Sergiyovych Myroshnychenko, Galyna Mykolayivna Saldan, Vitaliy Leonidovych Levinskiy, Olexiy Oleksandrovych Lyubchenko. Clinical and Morphological Features of Primary Pulmonary Hypertension: The Analysis of Two Cases from Practice. *American Journal of Internal Medicine*. Vol. 5, No. 6, 2017, pp. 112-116. doi: 10.11648/j.ajim.20170506.11

Received: April 1, 2017; **Accepted:** May 18, 2017; **Published:** October 26, 2017

Abstract: Primary pulmonary hypertension is a rare disease of unknown etiology, which is diagnosed in cases when examination of the patient with high blood pressure in the pulmonary artery does not allow determining its causes. The authors of this article analyze the literature data about primary pulmonary hypertension and report two cases from practice of this pathology. In one case of autopsy of 32-year-old woman primary pulmonary hypertension has been established during the investigation of autopsy material and in another case of autopsy of 52-year-old man this disease has been diagnosed during life. The description of the current state of the problem of primary pulmonary hypertension will be interesting to doctors of any specialization and will also allow to improve of physicians knowledge about this pathology.

Keywords: Primary Pulmonary Hypertension, Clinical and Morphological Features, Cases from Practice, Literature Review

1. Introduction

Pulmonary arterial hypertension is a threatening pathological condition characterized by a persistent increase of the blood pressure in the pulmonary artery vascular bed, which further leads to the development of right ventricular failure and the formation of pulmonary heart [1-3]. Pulmonary arterial hypertension is diagnosed in the case of increasing the mean pulmonary arterial pressure > 25 mmHg at rest or > 30 mmHg on exertion [3-4].

According to the modern classification of pulmonary hypertension, adopted at the 5th World Symposium on

Pulmonary Hypertension (Nice, 2013), there are such types of pulmonary arterial hypertension as: idiopathic (primary), hereditary, induced by intake of drugs and toxins, associated with connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, chronic hemolytic anemia [5-6].

Pulmonary arterial hypertension is a rare disease and comprises, for instance, 15 cases per 1 million people in France, 16 cases per 1 million in Spain, 41-45 cases per 1 million in the United Kingdom [4]. Primary (idiopathic) pulmonary hypertension is the most frequently observed among all forms of pulmonary arterial hypertension, the share

of which, according to different scientists, ranges from 39.2% to 50.0% of cases [1-4].

Primary pulmonary hypertension is a disease of unknown etiology, which is diagnosed in cases when examination of the patient with high blood pressure in the pulmonary artery does not allow determining its causes [3]. In other words, primary pulmonary hypertension is an independent disease which is not associated with cardiac or pulmonary pathology and based on the organic changes in the pulmonary vessels leading to the rise of pulmonary vascular resistance and pressure in the pulmonary circulation [7-10].

Primary pulmonary hypertension is more common in women than men (the ratio is 2:1 or even 4:1) aged 20 to 40 years [3, 11]. Some authors describe the cases of this disease in infants [4, 12].

Pathomorphological picture of pulmonary arterial hypertension was firstly described by German pathologist Ernst von Romberg in 1891. In 1901 an Argentinian doctor Abel Ayerza found that an aggregate of such clinical manifestations as chronic cyanosis, dyspnea and polycythemia were associated with sclerotic changes in the pulmonary arteries at autopsy. F. C. Arrillaga, one of the students of Abel Ayerza, called later this syndrome «Ayerza's disease». It was established later that the signs of pulmonary hypertension in that was patient was associated with syphilitic disorder of the lungs so the term «Ayerza's disease» is not used in practice since then [1, 10].

Triggering factors in the pathogenesis of primary pulmonary hypertension are still not fully understood. Many scientists reckon that endothelial dysfunction of pulmonary vessels plays an important role in the development of this disease, causing the imbalance in «vasodilatation-vasoconstriction» system, the reduction of pulmonary vascular bed, the decrease of elasticity of the lung vessel walls and obliteration of their lumen, particularly the distal pulmonary arteries, making them prone to thrombosis, proliferation, fibrosis of smooth muscle cells, local inflammatory reactions, accompanied by increased levels of proinflammatory cytokines and the disruption of serotonin metabolism in platelets. An important role belongs to the increased expression of angiotensin-converting enzyme involved in the formation of angiotensin II and the development of intimal lesions, contributing to the progression of vascular remodeling processes. Local thrombosis of small pulmonary arteries is another factor triggering the development of hypertension [6, 13].

The diagnosis of primary pulmonary hypertension is extremely difficult and unfortunately in some cases this pathology is diagnosed during the study of autopsy material. Primary pulmonary hypertension is characterized by gradual, imperceptible onset and further progression of the disease. The diagnosis is established approximately in 2 years after the onset the symptoms which in most cases are non-specific: shortness of breath, tiredness, chest pain, palpitations, syncope, Raynaud's syndrome. During examination the patients it is possible to reveal the amplification of pulmonary component of the 2nd tone with its reduction of cleavage

above the pulmonary artery. In 80% of patients palpation reveals the right ventricle push to the left of the lower sternal border and in 40-70% auscultation detects the systolic murmur of the tricuspid insufficiency. In rarer cases examination shows swelling of the neck veins, enlarged liver, peripheral edema, right ventricular gallop rhythm and Graham Steell murmur [11]. Apart from the assessment of medical history, clinical symptoms and physical examination findings, verification of primary pulmonary hypertension diagnosis requires additional examination, such as electrocardiography, chest X-ray, echocardiography, right heart catheterization, vasoreactivity test [1, 6].

Morphological diagnosis of primary pulmonary hypertension is based on the clinical data, results of histological examination of biopsy or autopsy material. In order to establish the correct intravital pathohistological diagnosis of primary pulmonary hypertension it is important to conduct open or videothoroscopic lung biopsy of lung tissue volume is not less than $2.0 \times 2.0 \times 1.5$ cm, preferably from the lower lobes, because in these areas there are numerous vessels, while in the upper and middle lobes can occur nonspecific intimal fibrosis. According to the pathohistological features there are four types of idiopathic (primary) pulmonary hypertension: plexogenic pulmonary arteriopathy, recurrent pulmonary thromboembolism, pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis [7].

Plexogenic pulmonary arteriopathy in the initial stages of the disease is characterized by hypertrophy of the muscular layer of arterioles and small branches of the pulmonary artery. Further progression of the disease contributes to intimal proliferation with fibroelastosis that leads to narrowing of the vessel lumen. Plexogenic structures are formed proximal to the obliteration site associated with the intimal fibroelastosis. Plexus structure is represented by branching vessels with thin walls, single elastic membrane and proliferating endothelial cells [7, 8].

In recurrent pulmonary thromboembolism the greatest changes occur in the arterioles and branches of the pulmonary arteries. In the vascular lumen there are thrombi in various stages of organization. It is possible recanalization of the thrombus with the focal eccentric intimal fibrosis [7, 8].

Pulmonary veno-occlusive disease is triggered by proliferation and fibrosis of the intima of the pulmonary veins and venules with the complete occlusion of the precapillary arterioles. In veins are found fresh, organized and recanalized thrombi. The restructuring of the veins implies their arteriolization in the form of hypertrophy of the muscular layer [7, 8].

Histological examination in pulmonary capillary hemangiomatosis detects the proliferation of the capillaries of interalveolar septa with the formation of a double layer on both sides of the septa, an increase the number of capillaries in perivascular and peribronchial connective tissue, pleura and pulmonary vein walls with the destruction of elastic tissue and obliteration of the lumen. Other findings include interstitial fibrosis and nonspecific hemosiderosis [6-8].

At the present stage statistical data about the survival of the patients with primary pulmonary hypertension are disappointing: the life expectancy after the diagnosis ranges from 6 months to 6 years, which, as noted by researchers, is comparable with the prognosis at oncologic diseases [1, 9, 13, 14].

Pregnancy and childbirth significantly increase the burden on the heart so the primary pulmonary hypertension is considered as the main contraindication for pregnancy. However if pregnancy occurs fatal outcome is observed in over 60% of cases usually in the early postoperative period [11].

Considering the rarity and relevance of primary pulmonary hypertension we present to the medical community clinical and morphological analysis of two cases from practice of this disease.

2. Case Report

In the first case a 32-year-old woman was in the hospital for 13 hours. On admission the patient complained of general weakness, dizziness, feeling of air lack. It is known from anamnesis that these symptoms appeared a month ago from the moment of admission to the hospital. During objective examination it was noted serious condition of the patient, passive position, shortness of breath up to 30 breaths per minute, pale skin and visible mucous membranes. Hemodynamics was with the tendency to hypotension (blood pressure was 80/40 mmHg). Auscultation determined harsh breathing throughout the lungs on both sides. Heart sounds were muffled and rhythmic. Chest X-ray in a forced horizontal position showed a decreased transparency of the pulmonary tissue of low intensity in the left lung; the heart and aorta were without impairment. During examination the patient by vascular surgeon it was suspected pulmonary embolism and deep vein thrombosis of the right lower limb. Ultrasound examination determined expansion of the cavities of both atria, right ventricular hypertrophy and signs of pulmonary hypertension. Angiopulmonography showed occlusive thrombus of the lower lobar branch of the left pulmonary artery, non-occlusive thrombus in the lower lobar and middle lobar branches and occlusive thrombus of the upper lobar branch of the right pulmonary artery. After the angiopulmonography it was administered urgent thrombolytic therapy. In spite of the conducted therapy condition of the patient progressively deteriorated. It was observed stopping of three times of effectively blood circulation and the patient died.

The final clinical diagnosis was formulated as follows: the main disease – embolism of pulmonary artery, deep vein thrombosis of the right lower limb; the cause of death – thromboembolism of pulmonary artery; the complication of the main disease – pneumonia of the lower lobe of the left lung.

At autopsy external examination of the body showed that skin and visible mucous membranes were of pale gray color with expressed cyanosis of nasolabial triangle. Lungs were heavyweight, in some places of airy-dough consistency, in other ones of dense consistency. On the cross section the lung tissue was pink color and on the areas of indurations it was dark red color. Pulmonary arteries were with extended lumen, their walls were dense and thickened, in the lumens of small branches of the pulmonary artery were determined attached to the vessel wall mixed thrombi, which in some places totally and in other ones subtotally obturated the lumen of the vessel. The heart was enlarged in size (heart weight was 420 g) mainly due to right parts of the heart, the right ventricle and atrium were expanded. The thickness of the wall of the right ventricle was 0.80 cm, the left ventricle – 1.20 cm. Ventricular index was 0.82. Papillary and trabecular muscles were hypertrophied mainly in the right ventricle. Other organs and vessels of the lower extremities were without macroscopic changes.

Histological examination of the autopsy material in the lung tissue fragments showed expressed structural changes in arterioles and small arteries, characterized by intimal thickening due to the presence of fibroblastic differon cells and connective tissue fibers, resulting in the narrowing of the vessel lumen; increasing the media due to smooth muscle fibers hypertrophy and hyperplasia and excessive growth of connective tissue fibers; thickening of the adventitia with perivascular sclerosis (figure 1). In the lumen of numerous vessels there were thrombi in various stages of organization with the presence of infarctions in some fields of view in the surrounding lung tissue characterized by necrosis with shadows interalveolar septa and hemorrhage. Capillary network of interalveolar septa was characterized by uneven hyperemia. In some fields of view in the pulmonary tissue were found the areas of sclerosis, which had likely resulted from previous pulmonary infarction (figure 2). Besides, there was edematous fluid in the lumen of some alveoli. In the fragments of the heart tissue the cardiomyocytes hypertrophy were observed, the most severe in the right ventricle, perivascular and intermuscular cardiosclerosis. In the liver tissue moderate degenerative changes of hepatocytes, a slight expansion of portal tracts due to connective tissue and moderate lymphoid-macrophage infiltration were determined. There were no microscopic changes in other organs.

Clinical findings, autopsy and microscopic examination of autopsy material allowed to establish pathoanatomical diagnosis: the main disease – primary pulmonary hypertension with the formation of pulmonary heart, thrombosis of the pulmonary artery branches and pulmonary infarctions; the cause of death – pulmonary-heart insufficiency. Comparison of the clinical and pathoanatomical diagnoses showed their disagreement due to the short duration of the patient in the hospital.

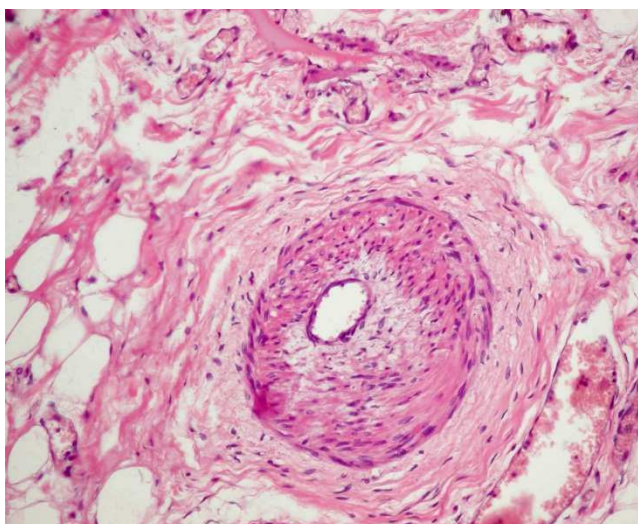


Figure 1. Thickening of the vascular media and adventitia with the perivascular sclerosis. (Hematoxylin & eosin stain, $\times 200$).

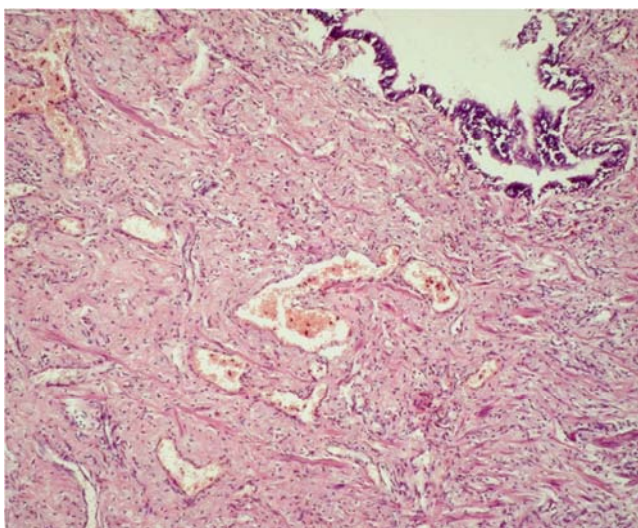


Figure 2. The area of sclerosis in the lung tissue. (Hematoxylin & eosin stain, $\times 100$).

In the second case a 52-year-old man was in the hospital for 3 days. On admission the patient complained of shortness of breath at minimal physical activity within the bed, general weakness, lack of appetite, unproductive cough. From anamnesis it is known that there was shortness of breath during physical activity a year ago. On admission to the hospital the patient's condition was of moderate severity. Skin and visible mucous membranes were pale, with expressed cyanosis of the lips, acrocyanosis. Percussion above the lungs detected lung sounds with boxed shade. Auscultation identified vesicular breathing evenly weakened above the lungs surface. Echocardiography established the dilatation of the right parts of the heart. Coronary angiography with the probing of the cardiac cavities determined pulmonary hypertension. According to results of complex examination of the patient primary pulmonary hypertension was diagnosed. However, despite the given treatment, the patient's condition progressively deteriorated and he died.

Autopsy showed enlarged and thickened of the pulmonary

arteries with the presence in some of them obstructive thrombi. The heart was enlarged in size (heart weight was 480 g), mainly due to the right parts of the heart, the right ventricle and atrium were expanded. The thickness of the wall of the right ventricle was 0.90 cm, the left ventricle – 1.30 cm. Ventricular index was 0.85. Examination of other organs and systems did not show any macroscopic changes.

Histological examination of autopsy material allowed to reveal in the pulmonary tissue more expressed structural changes in arterioles and small arteries in comparison with the first case characterized by intimal hyperplasia, media hypertrophy, adventitial proliferation, resulting in vascular lumen narrowing. Medial hypertrophy in a number of small arteries was so pronounced that by their volume these vessels resembled medium caliber arteries. In the lumen of some arteries fresh or organized thrombi were identified (figure 3). In the lung tissue there were also hemorrhagic infarctions and areas of sclerosis the number of which was larger in comparison with the first case. The examination identified hypertrophy of cardiomyocytes in the cardiac tissue more expressed in the right ventricle and sclerotic changes.

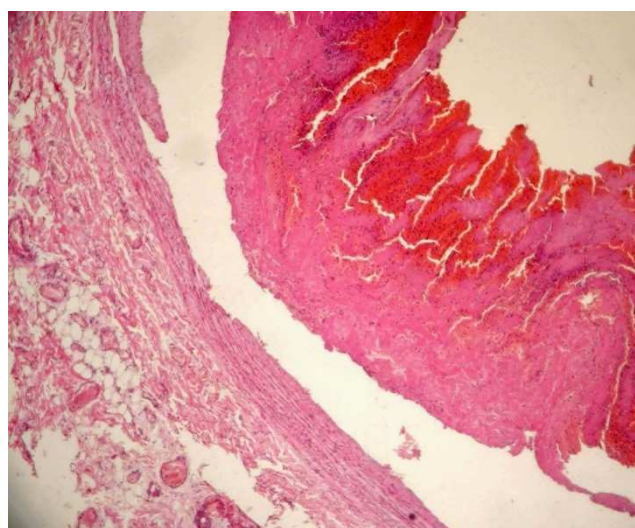


Figure 3. Mixed thrombus in the lumen of the vessel. (Hematoxylin & eosin stain, $\times 40$).

Clinical findings, the results of autopsy and microscopic examination of autopsy material allowed to define the pathoanatomical diagnosis: the main disease – primary pulmonary hypertension with the formation of pulmonary heart, thrombosis of the pulmonary artery branches and the development of pulmonary infarctions; the cause of death – pulmonary-heart insufficiency. Comparison of the clinical and pathoanatomical diagnoses identified their agreement.

3. Discussion

This clinical and morphological analysis of two cases from practice suggests that primary pulmonary hypertension is the difficult diagnosable disease with the unfavorable prognosis. Determination of the morphological changes during the study of biopsy or autopsy material is the basis for understanding the

development of primary pulmonary hypertension.

The analysis of literature data and own cases from practice suggests that primary pulmonary hypertension is characterized by primary morphofunctional changes in the pulmonary vessels (arterioles, arteries of small and sometimes of medium-caliber), which leads to the reduction of their cross-sectional area and the development of hypertension in the pulmonary circulation. It has been proved that the severity of changes in vascular walls in primary pulmonary hypertension does not depend on the disease duration and increases with the pulmonary arterial pressure increase [8]. The hypertrophy of the right ventricle of the heart develops as the result of hypertension in the pulmonary circulation which bears the name of pulmonary heart [1, 2].

The conducted macroscopic and microscopic study of the lung tissue fragments allowed to reveal in both cases the combination of specific features for plexogenic pulmonary arteriopathy and recurrent pulmonary thromboembolism. Some scientists reckon that the separation of primary pulmonary hypertension on the plexogenic pulmonary arteriopathy and recurrent pulmonary thromboembolism is artificial, because these two types of primary pulmonary hypertension are the stages of the same process [6-8].

Modern methods of treatment can significantly reduce the clinical signs of primary pulmonary hypertension, increase the tolerance for physical loads, improve the life quality and prolong life expectancy of the patient [3, 15, 16].

4. Conclusion

The description of the current state of the problem of primary pulmonary hypertension with clinical and morphological analysis of two own cases from practice will be interesting to doctors of any specialization and will also allow to improve of physicians knowledge about this pathology.

References

- [1] Zhuravlyova LV, Filonenko MV, Lopina NA Pulmonary hypertension: a challenge of correct diagnosis. *Medicine of Ukrainian transport*. 2013; 2: 73-78.
- [2] Firth AL, Mandel J, Yuan J X-J Idiopathic pulmonary arterial hypertension. *DMM*. 2010; 3: 268-273.
- [3] Efremova OA, Logvinenko SI, Bocharova MA, Gubareva NA Rare case in practice of physician – primary pulmonary hypertension. *Scientific reviewing journal (Medicine. Pharmacy)*. 2011; 22 (117) (16): 281-284.
- [4] Humbert M, Souza R, Simonneau G Idiopathic pulmonary arterial hypertension and its prognosis in the modern management era in developed and developing countries. *Pulmonary Vascular Disorders*. 2012; 41: 85-93.
- [5] Hoette S, Jardim C, Souza D Diagnosis and treatment of pulmonary hypertension: an update. *J Bras Pneumol*. 2010; 36 (6): 795-811.
- [6] Camm AJ, Lüscher TF, Serruys PW, editors. *The ESC Textbook of Cardiovascular Medicine*. 2nd ed. Oxford: Oxford University Press; 2009. 1398 p.
- [7] Paltsev MA, Kaktursky LV, Zairatyants OV, editors. *Pathological anatomy: national leadership*. Moscow: GEOTAR Media; 2011. 1264 p.
- [8] Batman YuA, Volos LI Morphologic features of lung vessels at hypoxia due to primary pulmonary hypertension. *Bulletin of urgent and recovery medicine*. 2003; 8 (3): 402-405.
- [9] Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *European Respiratory Journal*. 2010; 36 (3): 549-555.
- [10] Senatorova A, Gonchar M, Boichenko A, Strashok A Primary pulmonary hypertension in children. *Health of the child*. 2007; 2 (5): 166-170.
- [11] Guryanov VA, Tolmachev GN Primary (idiopathic) pulmonary hypertension (Ayerza-Arrillaga syndrome) and pregnancy – intensive care and management. *Anesthesiology and reanimatology*. 2014; 59 (6): 56-60.
- [12] Sudakova NM, Gaplevskaya VF, Grevtseva NI, Trunova RB Ayers syndrome in child of the first year of life. *Pediatrics*. 2006; 6: 122-124.
- [13] Porodenko NV, Skibitskiy VV, Zapevina VV The diagnosis and treatment of pulmonary hypertension: a modern view on the problem. *Kuban Research Medical Herald*. 2014; 3 (145): 140-144.
- [14] Garkina SV, Adonina EV, Duplyakov DV, et al. Patient with primary pulmonary hypertension – who is he and how to help him? *Clinician*. 2011; 3: 103-105.
- [15] Ataya A, Cope J, Hassan A A review of targeted pulmonary arterial hypertension – specific pharmacotherapy. *J. Clin. Med*. 2016; 5, 114: doi: 10.3390/jcm5120114.
- [16] Rich JD, Rich S Clinical diagnosis of pulmonary hypertension. *Circulation*. 2014; 130: 1820-1830.