Bronchopulmonary and Cardiovascular Pathology in Asthmatic Patient with Paecilomycosis

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Research

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Abstract

Background: This research aims to investigate the role of *Paecilomyces* fungus infection in pathologies of bronchopulmonary and cardiovascular systems in patients having bronchial asthma.

Methods: Histopathological study of lungs and cardiac tissues, in patients having bronchial asthma and *Paecilomyces* infection, were studied based on 15 autopsies: 5 women and 10 men, aged between 18 and 77 years, who died of intractable asthma attack and acute cardiovascular insufficiency. All the histological, histochemical, morphological, bacteriological and mycological examinations were performed. Paraffin sections from different tissues were stained with hematoxylin and eosin, and differential methods were used to detect fungi in the tissue.

Results: Microscopic examination in the lungs revealed the following observations: vascular congestion, extension of venules and capillaries, spasm of arterioles, swelling of endothelial cells with a tendency to desquamation and increased permeability of the vascular wall with fungal cells in the perivascular space. Changes in vascular walls were characterized by a pattern of destructive and productive vasculitis at different stages of development from endovasculitis to panvasculitis resulting in sclerosis. The same type of changes was found in vascular walls of heart tissues and tissues of other organs, distinguished only at different times. Sclerosis of the vascular wall and perivascular tissue are manifestations of the inflammatory protective response of the host organism, limiting the further spread of the pathogen in the organ tissues.

Conclusions: The development of combined vascular pathology of the bronchopulmonary and cardiovascular systems in bronchial asthma is triggered by hematogenic infection caused by dimorphic *Paecilomyces* fungi.

Background

The issue of hemodynamic abnormalities in bronchial asthma is still challenging nowadays. According to recent studies, the presence of hypertension in patients with bronchial asthma increases the probability of coronary complications. At the same time, many aspects of their etiology and pathogenesis remain undetermined. Furthermore, associated diseases of the cardiovascular system dominate over the exacerbating factors of bronchial asthma [1–5]. Numerous hypotheses have led to believe that development of hypertension directly correlates to infectious nature of the disease. Recently, *Paecilomyces* fungi with dimorphism and potentially pathogenic properties were discovered as a new type of causative pathogen of chronic persistent blood fungal infection. These results contribute to a new way of addressing our current research. According to the world literature, *Paecilomyces* fungi cause the development of systemic fungal infection in persons with both weak and also properly functioning immune systems [6–8]. Clinical manifestations of *Paecilomyces* infection are polymorphic [9–17], with dominating allergic symptoms and bronchial asthma [18]. The metabolic composition of the mycelium and liquid culture of *Paecilomyces variotii*, which was taken from the patient's blood, was represented by

free fatty acids and phospholipids, among which was the lysophosphatidylcholine. This has membranotoxic properties, which has a cytopathogenic impact on host cells [19, 20]. The experimental reproduction of *Paecilomyces* has shown the development of chronic alternative and productive inflammation in the lungs of test animals. Hence, vessels and bronchi get involved in the pathological process [21, 22].

This research aims to investigate the role of *Paecilomyces* fungus infection in the bronchopulmonary and cardiovascular pathologies in patients with bronchial asthma.

Patients And Methods

Histopathological examinations of bronchopulmonary and cardiovascular systems in patients with bronchial asthma with *Paecilomyces* infection were studied. The first phase of this study was permitted by the Academic Council of Sechenov University to be carried out on 15 autopsies of 5 women (aged between 18 and 68 years) and 10 men (aged between 43 and 77 years).

Paecilomyces infection was established based on the results of microscopy of smears of peripheral blood and sputum. Analysis was carried out by the method of express diagnosis of *Paecilomyces* fungus with direct quantitative counting of mature spherules of the *Paecilomyces* fungus in 1 μ l of blood together with isolating the culture of the fungus and serological studies. In addition, a complex of histological, histochemical, morphological and bacteriological studies was used. Paraffin sections from different tissues were stained with hematoxylin and eosin, and other differential methods were used to detect fungi in the tissue (Mac Manus, Gridley and Gram-Weigert) [23]. The histopathological studies were carried out with a light microscope Leica DM1000 (Germany). Various specialists including cardiologist, pulmonologist and allergologist monitored and evaluated all the patients before death for an asthma attack, hypertension and heart diseases.

All patients passed away from suffocation caused by asthmatic attack due to the activation of *Paecilomyces* infection in the blood, induced by acute respiratory viral infection. In 13 patients (74%), bronchial asthma was combined with coronary heart diseases and cardiosclerosis.

The study was carried out at Sechenov University, Moscow City Clinical Hospital named after S.S. Yudina, and the Diagnostic Center (Center for Laboratory Research) of the Department of Health in Moscow.

Results

The histological pattern of changes in the lungs was polymorphic. It was caused mainly by changes in the blood vessel walls, perivascular and interstitial tissues. The walls of the bronchi were spasmodic or obturated with thick mucus in the form of mucous plugs. The swelling of the mucous membrane was detected with an exponential thickening of the basal membrane. Although, there was a thick infiltration in all layers of the bronchi, around this area eosinophils, lymphocytes, histiocytes and plasma cells were detected in thickness of these layers. Mucous plugs were

contained cells of the desquamated bronchial epithelium, eosinophils, macrophages and spherules of the *Paecilomyces* fungus.

In the same visual fields of pulmonary parenchyma, an uneven thickening of the interalveolar septum was found, together with pronounced plethora of blood vessels (Fig. a) and individual foci of hemorrhage. Also, vessel walls were thickened. There was evidence of swollen vascular endothelium and desquamation of endothelial cell as well as fragmented internal elastic membrane and increased permeability of vascular walls and perivascular edema (Fig. b). There were fungal cells found in erythrocyte thrombi, vascular walls and the perivascular space. In the lumen of the alveoli, it was observed a pale pink transparent liquid with an admixture of desquamated epithelium and leukocytes. Minor macrophage-histiocytic infiltrates were found in the tissues around the vessels and bronchi, which contained round-oval corpuscles with a two-contour capsule with dimensions of 5.0×5.0 to $29 \times 30 \mu\text{m}$ and even larger, which gave a positive color to fungi (Fig. c). In other visual fields, the interalveolar stroma was thickened; its infiltration from cells was more pronounced. Separate walls of small arteries and veins were seen in the form of fibrinoid swelling or fibrinoid necrosis. The changes in the walls of small and medium vessels were characterized by a pattern of destructive-productive vasculitis at different stages from endovasculitis to panvasculitis. This happened with increased permeability of their walls and efflux of fungal cells into the perivascular space. The cellular composition of infiltration around fungal cells was represented by activated eosinophils, lymphocytes, histiocytes and plasma cells. In three cases, a lymphatic and histiocytic infiltration with formation of granulomas without signs of caseous decay was revealed. The structure of granulomas was represented by single giant polynuclear cells, in which cytoplasm contains tissue forms of fungi or their cytoskeletons with granular contents. These were surrounded by epithelioid cells, macrophages and lymphocytes or by a thin layer of histiocytes and lymphocytes. In addition, areas of pulmonary parenchyma with connective tissue growth and stroma were observed around the vessels in peribronchial space as well as in the walls of the alveoli. Cellular response developed in lung tissues where fungal cells existed. This had a profile of alterative and productive inflammation with a tendency to a protracted course, resulted in sclerosis of the affected area, which caused limitation in the further spread of fungal cells into the organ tissues (Fig. d). It should be noted that along with pronounced histological changes in the lungs, there were areas where morphological disorders were minimal or completely absent, which indicated a disseminated nature of the lesion.

The generalized spread of *Paecilomyces* infection caused dissemination of the *Paecilomyces* pathogen in the tissues of various organs through the affected vessel walls which were mainly in small and medium caliber.

Histological sections of the heart muscle revealed changes in different times. In some visual fields, there was an edema of the interstitial stroma with the separation of fibers and necrosis of separate muscle fibers. In the lumen of the vessels, fungal tissue cells at different stages of development were observed (Fig. e). In other visual fields, focal infiltrates around small and medium vessels with destruction of the
fibrinoid swelling or fibrinoid necrosis and pronounced lymph-

plasmocytic infiltration in the perivascular area. Additionally, some areas with the growth of fibrous tissue between the muscle fibers and vessels up to their complete obliteration were observed (Fig. f).

Discussion

Arterial hypertension occurs in 65.1% of patients with bronchial asthma, which is significantly higher than in the total population. Studies of vascular structure and endothelial function in patients with arterial hypertension and bronchial asthma revealed signs of injury in the vascular wall, together with endothelial dysfunction which results in increased arterial stiffness when the disease becomes more severe [24, 25].

To date, the histopathological profile of changes in the tissues of various organs in Paecilomycosis has been poorly studied. According to Uys et al. [26], patients who passed away from septic endocarditis resulted from *Paecilomyces variotii* infection had infarct in their brain, kidney and spleen at various time span. Branched mycelium and spores in the blood clot enveloping the mitral valve prosthesis were found in histological samples that were stained with hematoxylin and eosin after infarct. Some of the spores were attached to the mycelium branches. Spores and mycelium were not stained, but their outlines were marked. As a result of argyrophilia, they were stained with silver nitrate (Gomori). Isolated spores without argyrophilia were found near this area. In the place where the thrombus is attached to the heart tissue, a cluster of histiocytic and epithelioid cells with giant multinuclear cells in between was revealed. In the cytoplasm of giant multinuclear cells, phagosomes with elements of fungal cells were discovered. In smears of the affected tissue, oval gram-positive bodies resembling yeast cells were observed; however, it was without any budding signs.

The available data obtained during the experiment [21] revealed a picture of systemic mycosis with a predominant lesion of the bronchopulmonary system. Changes in the lungs were characterized by injuries in the vessels and bronchi, accompanied by a response of the reticuloendothelial system in the form of lymph adenopathy, hepatomegaly, and splenomegaly. Fungal tissue forms represented by rounded-oval cells 2–5 microns in diameter, were located mainly in the interalveolar tissue, around the bronchi and blood vessels as part of cellular infiltrates and were colored in dark pink to purple (Gridley) and in brown-black colors (Gomori-Grocott). These fungal tissue forms had a double circuit shell with a cellular structure. The mycelial phase of fungus development in tissues has not been established.

According to the results of our own study of the lungs, the following were evident: vascular congestion, extension of venules and capillaries, spasm of arterioles, swelling of endothelial cells with a tendency to desquamation and increased permeability of the vascular wall with the efflux of fungal cells in the perivascular space. Changes in vascular walls were characterized by a pattern of destructive and productive vasculitis at different stages of development from endovasculitis to panvasculitis with a sclerotic outcome. Changes of the same type were found in vascular walls in heart tissues, which were distinguished only by the time of their occurrence. Sclerosis of the vessel wall and perivascular tissue were the manifestation of protective inflammatory reaction of the host organism, limiting further spread of the pathogen in the organ tissues.

Conclusions

1. The development of combined vascular pathology of the bronchopulmonary and cardiovascular systems in bronchial asthma is triggered by internal human hematogenic infection caused by dimorphic *Paecilomyces* fungi with potentially pathogenic properties.
2. Occasional outbreaks of *Paecilomyces* infection in the blood, with underlying transient immunodeficiency, trigger the development of a chronic inflammatory response in the blood vessel walls resulting in sclerosis and the development of hypertension, exacerbating the bronchial asthma progression with underlying *Paecilomyces*.

Declarations

. Ethics approval and consent to participate:

This study has been reviewed and received ethics clearance through the Sechenov First Moscow State Medical University (Sechenov University) Research Ethics Board and Moscow City independent Ethics Committee (Number 1476, 13.11.2019). The first phase of this study was permitted by the Academic Council of Sechenov University to be carried out on 15 autopsies of 5 women and 10 men. All efforts including consents have been made to ensure confidentiality of any identifying information that was obtained in connection with this research.

Studies involving animals: "Not applicable"

. Consent for publication:

All authors provided consent for publication.

. Availability of data and material:

The data analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests:

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The authors have no competing interests to declare.

.Author's Contributions:

Sizova Z.M. designed the study and took responsibility for the integrity and accuracy of the data, data analysis and critical revision.

Akhunov V.M. contributed to the study design, data collection, data analysis, data interpretation, and the writing of the manuscript.

Azimzadeh A.A. contributed to the coordination, data analysis and interpretation, and the writing of the manuscript.

Lavrentieva T.P. contributed to laboratory diagnosis, data analysis and interpretation.

All of the Authors read and approved the final manuscript.

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Figures

Figure 1

Interalveolar septum unevenly thickened. Some alveoli show atelectasis; others are dilated due to emphysema. There is an obstruction in the central part of the vessel by an erythrocyte thrombus, in which the composition of fungal cells is determined.

Figure 2

Endovascularitis of small vessels in the lung, in the lumen of which spherules are visible at different stages of development. Stained with hematoxylin and eosin. X 400

Figure 3

A mature spherule in the wall of the thickened interalveolar septum. Gram-Weigert stain. X900.

Figure 4

Sclerosis of the vessel wall and perivascular tissue. In the visual field, there is a single growth of a spherical against the background of numerous spores immured in the connective tissue with no signs of further development. Gram-Weigert staining. X400.

Figure 5

Edema of the interstitial stroma of the heart muscle, separation of fibers and necrosis of individual muscle fibers, fungal cells in the vessel lumen at different stages of development. Stained with hematoxylin and eosin. X400.

Figure 6

Growth of connective tissue around the vessel with complete obliteration of its lumen. Stained with hematoxylin and eosin. X200.