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## CLINICO-PATHOLOGICAL ANALYSIS OF A RARE CASE OF PULMONARY NOCARDIOSIS UNDER THE MASK OF DISSEMINATED TUBERCULOSIS

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*Nocardiosis is a rare infectious disease caused by bacteria of the genus Nocardia and characterized by the development of foci of purulent-necrotic inflammation of the lungs, brain, and internal organs. Clinical diagnosis of nocardiosis has objective difficulties.*

*The aim of the study is to highlight a rare clinical case of pulmonary nocardiosis, to analyze mistakes in the clinical diagnostics of the main disease, to discuss the differential diagnosis of nocardiosis.*

*Materials and methods.* A clinico-pathological analysis of an inpatient and outpatient medical record card, and the results of an autopsy of a 58-year-old patient who died in an anti-tuberculosis institution from pulmonary nocardiosis has been carried out.

*Results.* According to the anamnesis, the patient suffered from COPD and chronic polyposis rhinitis with hypertrophy of the nasal turbinates for many years. Polypectomy and submucosal resection of the nasal septum were performed in the otolaryngology department. Wegener's granulomatosis was suspected during the intravital pathomorphological examination of nasal polyps, and glucocorticoids were prescribed in the hospital. Histological preparations and biological material of the patient were examined in clinics in Berlin, the diagnosis of "Wegener's granulomatosis" was not confirmed, however, domestic doctors recommended Medrol, which the patient received continuously for 5 years at a dose of 12 mg/day.

After 5 years, the patient was admitted to the hospital of a specialized anti-tuberculosis institution in serious condition with a clinical diagnosis: newly diagnosed disseminated tuberculosis of both lungs with disintegration, right-sided spontaneous tension pneumothorax, respiratory insufficiency of the III degree. According to urgent indications, thoracentesis and drainage of both pleural cavities were performed. Despite intensive therapy, the condition worsened, and biological death occurred 11 days after hospitalization.

During the post-mortem pathological examination, signs of tuberculosis of both lungs were not detected, nocardiosis of both lungs was diagnosed, which pathomorphologically manifested as multiple foci of purulent-necrotic bronchopneumonia with disintegration. Pathological diagnosis was confirmed by bacteriological and PCR examination of the post-mortem material. The disease developed on the background of wrongly prescribed long-term glucocorticosteroid therapy, which was carried out for the misdiagnosis "Wegener's granulomatosis". No signs of Wegener's granulomatosis were found at autopsy. The direct cause of death was acute respiratory failure.

*Conclusion.* Thus, pulmonary nocardiosis was not diagnosed in the hospital, the reason for the misdiagnosis was the rarity of the disease and the objective difficulties of diagnostics. A decisive role in the development of nocardiosis was played by erroneously prescribed long-term glucocorticosteroid therapy, which should be considered as a pathology of the therapy

**Keywords:** nocardiosis, pulmonary, autopsy, clinico-pathological analysis, hyperdiagnosis, tuberculosis, glucocorticosteroid therapy

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### 1. Introduction

Nocardiosis (synonyms: streptotrichosis, cladotrichosis) – a rare infectious disease caused by bacteria of the Nocardia genus. Nocardia species are aerobic gram-positive, acid-fast actinomycetes. They do not form spores, capsule, and druses. Nocardia asteroides is responsible for most cases of nocardiosis. The bacterium was first described by French bacteriologist Nocard in 1888 [1]. To date, the existence of 109 different species

of Nocardia with confirmed names is known [2]. *Nocardia infections* is characterized by the development of purulent-necrotic inflammation of the lungs, brain, internal organs, rarely – skin, subcutaneous fat tissue, mucous membranes [3]. According to various estimates, several thousand new cases of nocardiosis infection are registered in the world every year [4]. More than half of nocardiosis cases are affecting individuals with pre-existing immune compromise, those on long-term treatment with

steroids and / or blood pathology, can also arise from single-gene inborn errors of immunity and patients with haematologic malignancies haematopoietic, stem-cell transplantation [2, 5]. Most cases of nocardiosis are found in the subtropics and tropics, in Mexico, India, Pakistan and Iran [2, 4].

In most cases, nocardiosis is difficult to diagnose [6, 7]. This pathology is usually treated as pneumonia, tuberculosis, bronchiectasis, pulmonary tumor [8, 9].

Herein, we report the pulmonary nocardiosis mimicking disseminated tuberculosis in patient, admitted to specialized anti-tuberculosis institution.

**The aim of the study** is to highlight a rare clinical case of pulmonary nocardiosis, to analyze mistakes in the clinical diagnostics of the main disease, to discuss the differential diagnosis of nocardiosis.

## 2. Materials and methods of the research

In the period 2020–2021 a clinical and pathological analysis of the medical record of inpatient and outpatient, the result of an autopsy of a 58-year-old patient who died in an anti-tuberculosis institution from pulmonary nocardiosis was carried out. To verify the diagnosis, histological, histobacterioscopic, cultural and molecular genetic analysis of post-mortem lung samples was performed.

The research was conducted in compliance with the Convention on Human Rights and Biomedicine developed by the Council of Europe, the Helsinki Declaration of the Ethical Principles for Medical Research Involving Human Subjects, with the BRISQ reporting guidelines and the Procedure for the removal of biological objects from the deceased, whose bodies are subject to forensic medical examination and pathological examination, for scientific purposes [10].

The clinico-pathological analysis approved by the Commission on Bioethical Expertise and Ethics of Scientific Research at the Bogomolets National Medical University (protocol No. 144, dated 29.03.2021).

## 3. Research results

*Patient, 58 years*, was hospitalized on May 7th at 17.10 by ambulance brigade to the emergency department of specialized anti-tuberculosis institution at regional hospital with the diagnosis: disseminated tuberculosis of both lungs with disintegration, right-sided spontaneous tension pneumothorax, respiratory failure III. The patient was transferred from the hospital, which admitted on May 7th at 08.10 complaining of an expressed dyspnea, dry cough, fever up to 38–39 °C, general weakness. The symptoms had started 7 days earlier and has gotten worse over 2 days.

Examination data: patient's condition is serious. Constitution is normosthenic. Skin and visible mucous membranes are pale. *Acrocyanosis* found on hands and feet. Peripheral lymph nodes are not enlarged. Right sided tympanites was revealed by percussion. Auscultation data – breathing is hard and dramatically weakened on the right. Vital signs are BP – 110/80 mmHg., RR – 36/min, pulse – 100/min. Heart tones are rhythmic, muffled. Tongue is clean and moist. Abdomen is soft, painless on palpation. Liver is palpated at the costal arch. The spleen is not enlarged. Pasternatsky symptom is negative

on both sides. Meningeal signs are negative. Stool and urine are normal.

Chest X-ray investigation revealed a collapse of the right lung due to right-sided pneumothorax. Blood tests showed: RBC – 4,5 t/l, Hb – 136 g/l, WBC – 22.5 g/l, young-3, stabs-32, segs-58, Lymphocytes-6, Monocytes-1, ESR – 67 mm/h. Biochemical blood test: glucose – 4.06 mmol/l, total protein – 50.0 g/l, bilirubin – 4.56  $\mu$ mol/l, AST – 0.36 mmol/l, ALT – 0.87 mmol/l, urea – 9.49 mmol/l, fibrinogen – 13.2 g/dl, HCT – 36 %.

According to the family history, the patient grew and developed in good material living conditions. There was no family history of tuberculosis, cancer pathology, sexually transmitted diseases and he denied risk factor behaviour. Allergic anamnesis is not burdened. Patient had a 15-year history of chronic obstructive pulmonary disease (COPD) exacerbations 2-3 times per year and was treated with dexazone, pentoxifylline, bronchodilator and mucolytic therapy. In addition, he had level 3 disability in COPD. He had no previous history of bronchial asthma. Also, he had been suffered with chronic sinusitis, polypous rhinitis with turbinate hypertrophy. 5 years ago, patient was treated for the exacerbation of left-sided chronic sinusitis in Otorhinolaryngology department at regional hospital where the left-sided sinusotomy was done. Post-operative samples of the left maxillary sinus, taken for biopsy investigation, revealed suspected Wegener's granulomatosis. Was treated with solumedrol, dexamethasone, infusion therapy in the Rheumatology department at regional hospital. Histological preparations and biological material of the patient were examined in clinics in Berlin, the diagnosis of "Wegener's granulomatosis" was not confirmed, however. It should be noted that the blood serum test was performed in the laboratory Medical Diagnostic Institute, Berlin. Anti-proteinase 3 antibodies, the most common target antigen associated with Wegener's granulomatosis, were not found. According to a prescription written by a rheumatologist patient took medrol every day: initial dose – 24 mg/day, maintenance dose – 12 mg/day.

Patient was brought to hospital for in-patients of specialized anti-tuberculosis institution in extremis at 17.10, emergency thoracocentesis and right-sided pleural drainage in the third intercostal space on the right midclavicular line were performed leading to a release in air and 300 ml of greyish pus-like odourless fluid. Infusion, detoxification, and antibacterial therapy were prescribed to the patient.

Drainage and intensive conservative therapy *stabilized the patient's hemodynamic status* and *improved* general condition. The next day, on May 8th the patient was discharged to general thoracic department. Air and 150 ml of fluid were induced from the drainage tube in the right pleural cavity during a cough.

Clinical diagnosis was established on May 9th: right-sided non-hospital pneumonia with abscesses formation, right-sided tension pyopneumothorax, right-sided *pleural empyema*, purulent intoxication, respiratory failure III. A control chest X-ray showed collapsed right lung and extra drainage of pleural cavity was performed through right VIII-th intercostal space at the back axillary line. In 1,5 hour after surgery, the patient's condition was getting worse, severe dyspnea and acrocyanosis

appeared. Objectively: RR – 36/min. Percussion revealed left-sided tympanitis. Auscultation revealed strongly *diminished left lung breath* sounds. Chest X-ray showed partial collapse of the left lung due to tension pneumothorax and the patient was treated by *chest* tube insertion of the left pleural cavity at 17.00. Air and grayish pus-like odorless exudates were removed. After drainage, the patient's condition has stabilized, and dyspnea has decreased. Further, air and fluid were induced from all 3 drainage tubes during a cough.

The results of microscopic examination of fluid from the right pleural cavity revealed neutrophilic leukocytes – 30–40 in the field of view. Bacterioscopic acid-fast bacilli examination (AFB) showed +++ bacilli.

Clinical diagnosis, based on the bacteriological examination of fluid, was established on May 16th: first diagnosed tuberculosis of both lungs (disseminated) Destruction+ MBT+ (in exudate) Smear+ C 0 Resist 0 Hist 0. Bilateral spontaneous pneumothorax, respiratory failure II-III. Patient was transferred to a specialized phthisiopulmonology department, where was treated with

anti-TB therapy: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S).

Bacteriological examination of sputum on May 10, 14 and 15 – acid-fast bacteria (AFB) were not found.

Despite intensive and anti-TB therapy, the patient's condition remained serious due to respiratory failure. From May 17th the patient was constantly in a humidified- oxygen mask. May 18th 14.30 patient died due to an increased sign of respiratory and cardiovascular failure on the 11<sup>th</sup> day of his stay in hospital.

The final clinical diagnosis: first diagnosed tuberculosis of both lungs (disseminated) Destruction+ MBT+ (in exudate) Smear+ C 0 Resist 0 Hist 0. (2012). Respiratory failure III. Diffuse pulmonary fibrosis in both lungs. Empyema in both pleural cavities (drained), AFB+ (in fluid). Heart failure, stage B. COPD: chronic obstructive bronchitis in exacerbation stage. Emphysema.

Autopsy revealed multiple lung acinar-nodose, polilobular and segmental grayish-whitish foci of necrosis with destruction and the formation of multi-chamber cavities, diameter from 2.0 till 5.0 cm (Fig. 1).



Fig. 1. The left lung at autopsy with damage centers and cavities

Sectional material from different parts of the lesions was taken for bacteriological examination (non-specific bacterial, fungal flora and to *Mycobacterium tuberculosis*, as well as molecular biological study using polymerase chain reaction – PCR).

Histological examination of the lungs revealed nonspecific suppurative-necrotizing bronchopneumonia with abscess formation, destruction, and the formation of cavities. Specific granulomatous inflammation which is characteristic lesion for tuberculosis was not found (Fig. 2).

During post-mortem morphological examination of both maxillary sinuses and nasal cavity, chronic non-

specific inflammation without granulomatosis and vasculitis was revealed.

Post-mortem samples of *lung tissue* was sent for *culture* and *revealed* the growth of *Nocardia asteroides*. Gram-stained histopathological sections revealed multiple Gram-positive bacilli – *Nocardia* (Fig. 3).

They also had a pale red colour by the Ziehl-Neelsen stain, which indicates acid-fast bacilli. However, lung tissue specimens were cultured-negative and PCR-negative for *M. tuberculosis*. DNA of *Nocardia* was detected. Identification of *nocardia* was carried out in the institution's laboratory in accordance with recommendations [1, 6].

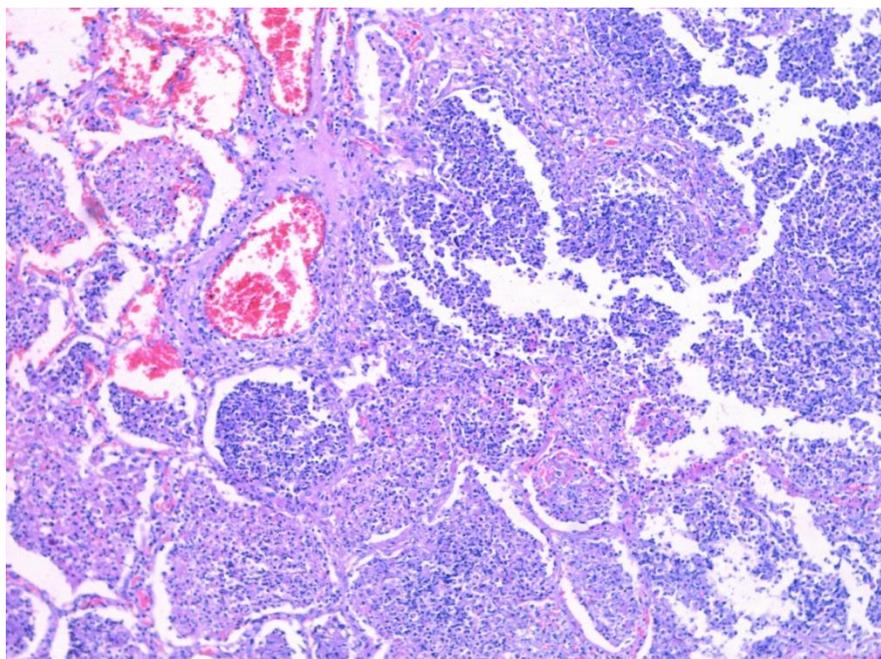


Fig. 2. Purulent-necrotic inflammation in the respiratory tract of the lungs. Hematoxylin-eosin stain,  $\times 100$

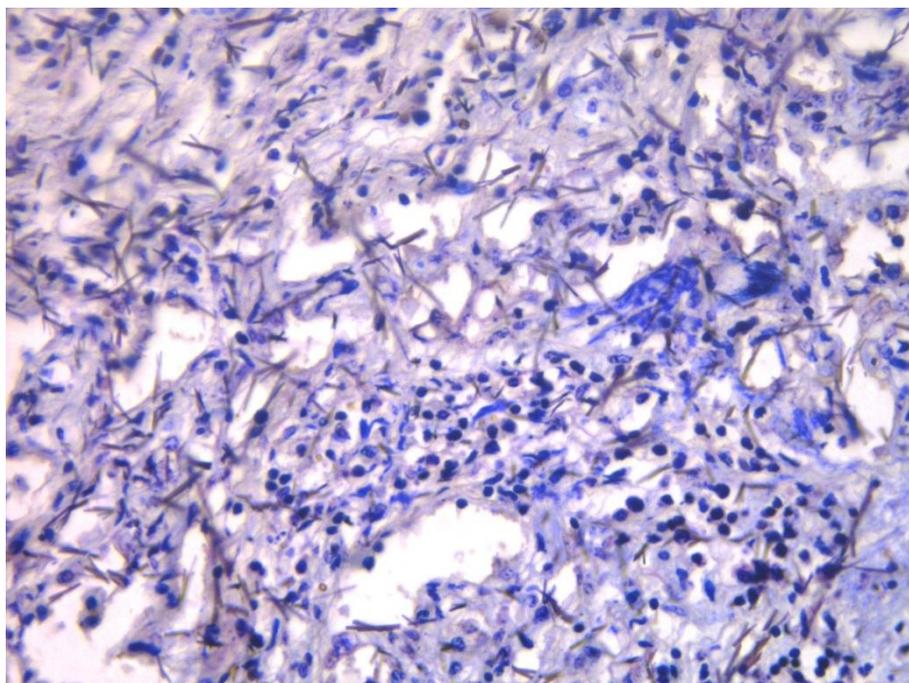


Fig. 3. Gram-positive nocardias in post-mortem lung samples. Histobacterioscopic analysis. Weigert-Gram stain,  $\times 400$

Based on a morphological, pathohistological, biological and molecular-genetic examination, pathological diagnosis was established:

I. Basic disease: Disseminated nocardiosis in both lungs.

Background state: Prolonged glucocorticosteroid therapy over due to probable "Wegener's granulomatosis".

II. Complications: Bilateral pyopneumothorax. Operations: right pleural cavity drainage; drainage of the left pleural cavity. Acute general venous hyperemia and alterative changes of the internal organs.

III. Concomitant diseases: Atherosclerosis of the aorta and coronary arteries. Chronic obstructive bronchitis. Chronic rhinosinusitis.

#### 4. Discussion

The incidence of diseases caused by *Nocardia* has increased over the past decades, due to improvements in identification methods, as well as increases in the immunocompromised population [2, 5]. Pulmonary nocardiosis develops as an opportunistic infection in a significant number of observations [9, 11].

According to the literature, pathogenic species of the genus *Nocardia* can be found in house dust, beach sand, garden soil, plants, and water. [1, 7]. Infection occurs by inhalation through the respiratory tract, through the gastrointestinal tract with contaminated food, with damage to the skin and mucous membranes. Pathogenicity for humans is quite low. Most cases of nocardio-

sis proceed according to the type of implantation disease, caused by pathogens entering the wound with soil and fragments of organic residues. Nocardiosis are not part of the normal human microflora, although they are sometimes isolated from clinically healthy individuals [1, 9].

After inhalation alveolar macrophages absorb the pathogen, where it is stored in their cytoplasm, inhibiting the synthesis of lysosomal enzymes and blocking phagosome-lysosomal fusions. Circulation of microorganism induces an inflammatory response (neutrophils, macrophages, lymphocytes), which leads to the formation of multiple drain abscesses. Nocardiosis affects the lungs in 2/3 of cases [12]. Often mediastinal organs, soft tissues of the chest, etc. are involved in the process. Disease is especially dangerous for individuals with immunodeficiency - organ and tissue recipients, patients with lymphoma, leukemia, pancytopenia, *dysgammaglobulinemia* and Cushing's syndrome. Life-threatening generalized forms of infection are accompanied by the development of meningeal syndrome, paralysis and paresis. Lesions of skin, kidney, liver, and lymph nodes are characteristic of disseminated nocardiosis. Subcutaneous fat tissue infections are usually initiated by local trauma, such as puncture wounds, and are accompanied by the formation of superficial pustules in the penetration site. With progression, clinical features resemble those of cutaneous actinomycosis and are accompanied by the formation of granulomas and abscesses [7, 11].

The main clinical form is pulmonary nocardiosis. The disease develops gradually, there is a weakness, malaise, increased night sweats, subfebrile body temperature. Patients have cough, initially dry, then with sputum (purulent with blood streaks). The body temperature gradually rises to 39-40 °C. X-ray imaging shows focal infiltrative changes of different size in lungs. The foci may merge, capture a segment or several segments of the lungs. Then collapse of pulmonary tissue develops with formation of multiple cavities. The pathological process from the lungs can move to the pleura, or mediastinal organs. Nocardiosis may be misdiagnosed as other infections, including nonspecific pneumonia with abscess formation, tuberculosis, or neoplastic process in the lungs [13, 14].

Hematogenous dissemination of the pathogen leads to the development of sepsis. Secondary septic lesions often occur in the brain [7, 8]. In addition, 30 % of all cases of pulmonary nocardiosis are complicated by central nervous system involvement and usually affect immunocompromised individuals. Skin lesions are more often localized on the distal surfaces of the lower extremities, where deep infiltrates, skin ulcers, non-healing fistulas, and cicatricial changes gradually develop.

There is a report in the literature about a case of pulmonary nocardiosis in an immunocompetent host, manifesting as a relapse of tuberculosis lungs [15]. In present case, pulmonary nocardiosis developed on the background of immunosuppressive condition due to prolonged glucocorticosteroid therapy and proceeded under the mask of a disseminated tuberculosis in both lungs. In an anti-tuberculosis institution, based on the examination of fluid from the right pleural cavity and detection acid-fast bacteria, clinical diagnosis of newly diagnosed tuberculosis of both lungs established. However, acid-fast bacteria were not found in the sputum. It is known that nocardia are acid-fast bacilli and have similar properties that are characteristic of other mycobacteria. The disease progressed and led to the death of the patient; the immediate cause of death was acute respiratory failure.

Signs of granulomatous inflammation were not detected at autopsy examination of lungs. Lung tissue specimens were culture-negative and PCR-negative for *M. tuberculosis*. Pathological diagnosis of nocardiosis was verified based on histobacterioscopic, cultural and molecular genetic analysis of post-mortem lung samples.

## 5. Conclusions

According to the presented clinical observation, the difficulties of verification of pulmonary nocardiosis were demonstrated which is associated with the rarity of the disease and the objective difficulties of diagnostics. A decisive role in the development of nocardiosis was played by erroneously prescribed long-term glucocorticosteroid therapy, which should be considered as a pathology of the therapy.

## Conflict of interests

The authors declare there is no conflict of interests.

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