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Slowly-resolving pneumonia

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Summary

Slowly-resolving pneumonia is an important medical problem in spite of current knowledge on etiology, pathogenesis and therapeutic approaches. In Russia, uniform approach to this disease is lacking. Risk factors for the slowly-resolving pneumonia are comorbidity, age, severity of the disease and certain pathogens. A wide range of infections and non-infection diseases resemble slowly-resolving pneumonia, such as autoimmune systemic diseases, interstitial lung diseases, drug-induced lung toxicity, thoracic tumours, tuberculosis, etc. A diagnostic algorithm has been described in the article aimed at identification of the pathogen causing the pulmonary inflammation and at exclusion of diseases mimicking slowly-resolving pneumonia.

Key words: slowly-resolving pneumonia, diagnostic algorithm, antibiotics, pathogen, antibacterial resistance, interstitial lung diseases.

Pneumonia is a disease of constant importance. The famous Russian physician of the XIX century S.P.Botkin in his clinical lectures showed prevalence of pneumonia in Saint-Petersburg in dependence on season, the patient's gender and social status. Today this is of great significance also. S.P.Botkin discussed a role of diplococci as a cause of pneumonia and some clinical issues, particularly slowly-resolving pneumonia.

Later, new pneumonia-causing pathogens were found and new clinical features were described. In middle 1950th, Mycoplasma pneumonia and Legionella pneumophila have been identified. Recently, new respiratory infection emergencies have been discovered. At the beginning of the XXI century, world medical community encountered an epidemic caused by an atypical coronavirus (SARS); two years ago the Middle-Asian coronavirus was identified. Since 2009 pneumonia prevalence has been growing, mostly due to associated viral and bacterial infection of the lower respiratory tract complicating influenza A (H1N1) disease. According to results of a large international survey on pneumonia epidemiology, such infection is identified in 3 to 5 persons per 1,000 of population. In 2013, the number of deaths from pneumonia in Russia increased by 8 %. Therefore, pneumonia is still one of the most widespread diseases with changeable etiology and the need of yearly characterization.

Physicians of different medical specialities such as general practitioners, infectiologists, pediatricians, neonatologists, pneumologists, hematologists, intensive care specialists, etc., could be involved in treatment of a patient with pneumonia. This affects the physician's approach to this disease partly due to different medical terms describing pneumonia: bronchopneumonia, croupous pneumonia, interstitial pneumonia, pneumonia in alcohol abuse patients, pneumonia in immunocompromised patients, focal pneumonia, slowly-resolving pneumonia. In Russian medical literature slowly-resolving pneumonia was studied by Prof. N.S.Molchanov and his follower Prof. V.P.Silvestrov, the author of a renowned monograph on this topic, the 4th edition of which was published in 1984. Since this time our knowledge on pneumonia has been dramatically improved.

The aim of this article was to emphasize the importance of slowly-resolving pneumonia and to highlight a role of Russian medical science in investigation of this issue.

According to the official data of the Russian Healthcare Ministry, yearly > 400,000 of patients seek medical care for pneumonia in 7th to 9th day of the disease, i.e. in presentation, in the great portion of the patients pneumonia is characterized by protracted course.

The current definition of slowly-resolving pneumonia is based on protracted or non-resolving inflammation with no response to therapy. This quite uncertain definition reflects a lack of evidence-based clinical trials of this problem. This definition also implicates that aspiration pneumonia and nosocomial pneumonia including ventilator-associated pneumonia, and pneumonia in immunocompromised patients do not pertain to slowly-resolving pneumonia. Diagnosis of slowly-resolving pneumonia is usually based on comparison with criteria of typical course (fever ≤ 2–4 days, cough ≤ 4–9 days, resolution of auscultative pneumonic phenomenon at the 1st week of the disease, decrease of blood leukocyte count to the normal level to the 4th day, decrease of C-reactive protein to the normal level to the 3rd day). Considering late start of the treatment in great number of patients mentioned above it become apparent the importance of slowly-resolving pneumonia in Russia.

Risk factors for the slowly-resolving pneumonia are comorbidity, age, severity of the disease and certain pathogens.

Comorbidity

Chronic obstructive pulmonary disease (COPD) is one of comorbidities that could increase risk of slowly-resolving pneumonia. Pneumonia could worsen the course of COPD and often has poor prognosis in these patients. Another risk factor is alcohol abuse related to decreased functional activity of macrophages, aspiration, mucociliary disturbance, and decreased cough reflex. Cough reflex depression is also seen in patients with neurological disorders.

Slowly-resolving pneumonia could develop in patients with congestive heart failure due to lymphatic drainage disturbance and in patients with chronic renal failure due to complement deficiency, decreased macrophage and

neutrophil functions and humoral immune insufficiency. Slowly-resolving pneumonia could complicate malignancy because of decreased immune function; moreover, chemotherapy facilitates airway colonization with different microorganisms. In patients with diabetes mellitus as well as in patients with AIDS slowly-resolving pneumonia could occur due to decreased neutrophil and cellular immunity functions and often leads to death.

Cellular or humoral immunity disorders could be an underlying condition in patients with slowly-resolving pneumonia. Patients with primary immunodeficiency suffer from recurrent pneumonias in childhood and lifelong recurrent respiratory infections affecting their quality of life.

The patient's age plays an important role in pathogenesis of slowly-resolving pneumonia. In patients < 50 years old radiological and morphological signs of pneumonia typically resolve in 4 weeks. In patients older 50 years resolution of pneumonia requires much longer time even in those without any comorbidity.

Pneumonia outcome is closely related to its severity. Resolution of severe pneumonia could require up to 10 weeks.

Pathogens

The leading pathogen causing pneumonia is Streptococcus pneumoniae. Typically, in pneumonia caused by this pathogen fever continues ≤ 2–3 days but in cases with multilobar lesions could persist up to 3 weeks as well as auscultative phenomenon in the lungs does. Antibacterial resistance of Streptococcus pneumoniae could also contribute to prolonged course of the disease. In Russia, antibacterial resistance is less common than in some European countries, such as France or Spain. Radiological signs of pneumonia caused by Streptococcus pneumonia could be seen up to 3 months, especially in bacteriemic patients. About $^1/_2$ of patients with pneumococcal bacteriemia have protracted course of the disease.

Slowly-resolving pneumonia caused by Legionella spp. could occur in elderly patients (> 65 years old), in smokers and in alcohol abusers. During outbreak of Legionella infection in Verkhnyaya Pyshma (2008), pneumonia was frequently complicated by nephritis, myocarditis, etc. Therefore, the experience of Legionella epidemics has shown that slowly-resolving pneumonia could lead to chronic extrapulmonary injury. Radiological disorders in such cases could persist for 1 year even in patients without purulent complications.

Compared to Legionella spp., Mycoplasma pneumoniae is a frequent cause of pneumonia but it is uncommonly could cause severe or slowly-resolving disease. Pneumonia caused by M. pneumoniae is typically resolved during 4 weeks but could be accompanied by bullous myringitis especially in children.

Chlamydophila pneumoniae cause pneumonia in young patients in > 30 % of cases and is characterized by mild to moderate course; severe disease is uncommon and could occur in patients with psittacosis. Such pneumonia is usually resolved in 3 months with rare abscessing forms.

Haemophilus influenza is a frequent cause of pneumonia in smokers, elderly patients and in patients with COPD. Recently, conjugated vaccine against H. influenza has been used in children; this resulted in reduction in the rate of childhood pneumonia caused by this pathogen.

According to results of epidemiological studies, only 50 % of pneumonia patients recover their lung function at 6 weeks.

Staphylococcus aureus, especially methicillin-resistant strains (MRSA), could often cause severe and abscessing pneumonia. Recovery in these cases could require 3 to 5 months with residual lesions in the lung tissue. Pneumonia caused by S. aureus could complicate acute viral respiratory infections (influenza) and cystic fibrosis in infants.

Gram-negative microorganisms are a frequent cause of nosocomial pneumonia and pneumonia in immunocompromised patients. These pathogens could cause slowly-resolving pneumonia lasting for 3 to 5 months with residual injury of the lungs after clinical recovery.

Moraxella catarrhalis is not a typical pathogen in patients with severe or slowly-resolving pneumonia but radiological pneumonic signs could be seen ≥ 3 months. Chronic inflammation rarely occurs in pneumonia caused by M. catarrhalis.

Tuberculosis (TB) infection can mimic slowly-resolving pneumonia. Diagnosis of TB is extremely difficult and often requires use of molecular methods (polymerase chain reaction, expert systems, etc.). This disease should be considered in high-risk patients including immigrants, elderly, immunocompromised patients.

Opportunistic and endemic fungal infection could initiate inflammation resembling slowly-resolving pneumonia. Fungal invasion particularly caused by Aspergillus could lead to necrotic lesions or to chronic course of the disease. Fungal infection is more common in patients with acquired immune deficiency or in patients receiving immunosuppressive therapy. Endemic fungal infections include histoplasmosis, blastomycosis, coccidioidomycosis. Pulmonary inflammation in these diseases resolves slowly.

Antibacterial resistance of pathogens such as S. pneumoniae, S. aureus, H. influenzae, Pseudomonas aeruginosa is greatly contribute to slowly-resolving course of pneumonia. In some regions antibiotic resistance of S. pneumoniae to cephalosporins and macrolides as high as 60 % with a consistent tendency to growing number of multidrug resistant strains. It is well known that laboratory findings do not consistently correspond to clinical data. Pneumonia caused by MRSA is typically characterized by severe course. Eradication of this pathogen especially in a hospital is one of the most important problems in preventing in-hospital infection. There is also a growing number of multi-drug resistant P. aeruginosa strains. Empiric antibacterial therapy for pneumonia requires recognition regional resistance of the most common pathogens with regard to previous therapeutic efficacy.

Concerns arise about pathogen resistance to new generations of antimicrobials, i.e. resistance of M. tuberculosis to old and new antituberculosis drugs and appearance

of pathogens with 100 % drug resistance, i. e. Burkholderia cepacia.

Thus, slowly-resolving pneumonia could be related to antibacterial resistance of the causative pathogen that can affect the outcome.

Currently, > 5 % of pneumonia cases are diagnosed in young patients with AIDS worldwide. This rate increases up to > 50 % in endemic regions, i. e. in equatorial Africa. Pneumonia in AIDS patients could be caused by pneumocystis, atypical mycobacteria, fungi. In patients with secondary immune deficiency pneumonia could be complicated by sepsis.

Differentiation

Slowly-resolving pneumonia should be distinguished with abscessing pneumonia and purulent complications, such as pulmonary abscess, empyema, pulmonary gangrene. These complications require special treatment approach.

Also, slowly-resolving pneumonia should be distinguished with benign or malignant neoplasms of the lung. Bronchogenic carcinoma could constrict airways leading to hypoventilation of the pertinent lung segments and then to atelectasis that could be an underlying condition for pneumonia development. Another malignancy that could be associated with focal pulmonary infiltration is bronchoalveolar carcinoma. Controversy between radiological findings and absent or very slight clinical signs of pneumonia are noted in this disease. Also, lymphomas could mimic slowly-resolving pneumonia. Clonal lymphoid proliferation could arise from the airway epithelium and sometimes is difficult for differentiation requiring lung tissue biopsy with further immunohistochemical examination. The lungs are involved in > 38 % of the cases of lymphoma. One of the most typical signs of lymphoma is hilar lymph nodes enlargement.

Endobronchial obstruction could be caused by carcinoid that is more prevalent is young patients. Lung involvement could occur in patients with autoimmune systemic diseases. Non-specific symptoms, such as fever, dyspnea and pulmonary infiltrates, are common in systemic vasculitis contributing to late diagnosis. Lung injury is generally seen in patients with Wegener's granulomatosis, polyangiitis and alveolar hemorrhage. Biomarkers for diagnosis of these diseases including anti-neutrophil cytoplasmic antibodies (ANCAs) for Wegener's granulomatosis and anti-erythrocyte antibodies for hemorrhagic pulmonary alveolitis are actively investigated.

Cryptogenic organizing pneumonia with bronchiolitis obliterans resembles slowly-resolving pneumonia. This disease is predominantly found in women. Main signs are fever, breathlessness and pulmonary infiltrates with failure of standard antibacterial therapy which should be discontinued and steroids should be administered in these patients.

Acute and chronic eosinophilic pneumonias have different pathogenesis. Acute eosinophilic pneumonia usually manifests with fever, dry cough and pleural pain. Radiological signs include diffuse ground glass opacity. The course of the disease is often severe; in some cases, acute respiratory distress syndrome could occur. Chronic eosinophilic pneumonia is effectively treated with steroids.

Acute interstitial pneumonia is a rare disease with progressive respiratory failure caused by acute respiratory distress syndrome; the disease is characterized by dramatic course during 2–3 weeks. The mortality as high as 70 %, effect of steroids is controversial.

Certain clinical variants of pulmonary sarcoidosis could also be difficultly distinguished with slowly-resolving pneumonia. In infiltrative pulmonary sarcoidosis, intrathoracic lymph nodes could have normal size. Transbronchial biopsy is of great importance for the diagnosis; in patients with sarcoidosis, typical granulomas could be found.

Pulmonary alveolar proteinosis is an orphan disease with lipoprotein deposition in the distal airways. Diffuse alveolar infiltrates are typically found in the chest X-ray. Diagnostic method is bronchoalveolar lavage (BAL) obtaining milky BAL fluid.

Among drug-induced lung injury, amiodarone lung toxicity is the most known. Clinical signs include fever, breathlessness and pulmonary infiltrates resembling pneumonia. Alveolar macrophages contain specific iodous inclusions.

Methotrexate is widely used in treatment of rheumatoid arthritis and could affect the lungs. This pulmonary disease should be distinguished with rheumatoid lung and slowly-resolving pneumonia. The accurate diagnosis is recommended because of different therapeutic approaches in these conditions. There is a large database on pulmonary injuries induced by nitrofurans and bleomycin. Bleomycin is widely used in experimental study to modeling pulmonary fibrosis. Current therapy of pulmonary fibrosis includes a large group of monoclonal antibodies that could modify the course of the disease but also could adversely affect the lungs. The main groups of monoclonal antibodies and their adverse effects are given below:

TNF-α inhibitors. Etanercept could induce pulmonary infections such as pneumococcal pneumonia, pulmonary tuberculosis, histoplasmosis, and non-infection disease such as lupus erythematosus with pleura involvement, pulmonary fibrosis, pneumonitis, worsening of interstitial lung disease. Infliximab could increase risk of tuberculosis, cryptococcosis, histoplasmosis, Legionella infection, actinomycosis, coccidioidosis and pneumonia caused by Pneumocystis jirovecii. Infliximab could also induce histiocytosis, drug-induced alveolitis, sarcoidosis, diffuse alveolar hemorrhage syndrome, pulmonary fibrosis, lupus erythematosus with the pleura and the lung parenchyma involvement. Tuberculosis and aspergillosis have been described to complicate therapy with adalimumab.

An interleukin-1 receptor antagonist anakinra could also increase risk of tuberculosis.

T-cell co-stimulation inhibitor abatacept has a potential adverse effect related to bacterial pneumonia occurrence.

Rituximab is a **chimeric monoclonal antibody** against the protein CD_{20}, which is primarily found on the surface of immune system B cells; adverse effects of rituximab are pulmonary fibrosis and interstitial pneumonia.

Therefore, new information on pulmonary involvement in drug metabolism has been gathered particularly regarding new generations of monoclonal and biological drugs. Lung tissue is very sensitive to these drugs and tuberculosis reactivation or other bacterial and fungal infections, autoimmune disease such as lupus erythematosus or interstitial pneumonia could occur in response to this therapy.

Slowly-resolving pneumonia requires to be differentiated from pulmonary embolism and pulmonary infarction. Every fifth case of pulmonary infarction is accompanied by pleural effusion and resolves for several weeks. Multiple pulmonary infarction foci could be complicated by abscessing pneumonia, mostly due to underlying airway colonization with S. aureus.

Congestive heart failure could facilitate development of pneumonia which is commonly slowly-resolving in these patients. Pneumonia in patients with congestive heart failure generally worsens the central hemodynamics and outcomes of congestive heart failure.

Diagnosis

Diagnostic algorithm in slowly-resolving pneumonia should include a detailed medical history and information on the regional epidemic situation. This is particular important in epidemic seasons of acute respiratory viral infections. In July, 2008, in Verkhnaya Pyshma thorough collection of epidemic data has provided successful diagnosis and treatment of pneumonia caused by Legionella related to operational problems in the local water uptake system. During the water uptake system repair domestic water was supplied from a local lake colonized with Legionella pneumophila that was the cause of the outbreak. The outbreak was localized in 3–5 days. When asking the patient a physician should consider a potential of having acquired immune deficiency especially in young patients. At presentation, it is extremely important to evaluate pneumonia severity because of a high probability of slowly-resolving course in more severe cases. The outcome of slowly-resolving pneumonia is greatly dependent on primary diagnostic algorithm including detection of co-morbidity (alcohol abuse, diabetes, cardiac disease, underlying chronic lung disease). This should be followed by the assessment of pneumonia resolution rate. Uncomplicated pneumonia course implicates resolution of the disease in 3–4 weeks. Otherwise, the diagnosis should be revised with focus on the pathogen identification and non-infection factors. Image methods including computed tomography (CT) and molecular tests could be useful. CT could reveal parenchyma abnormalities, emphysema, nodules, interstitial disease and evaluate extension of pulmonary inflammation.

Currently, novel diagnostic markers of pulmonary inflammation and molecular methods for pathogen identification have being searched. Measurement of serum procalcitonin and C-reactive protein has already become routine diagnostic tools. Therapy of slowly-resolving pneumonia should be changed according to results of the tests. If the reason of slowly-resolving course has been still unclear, bronchoscopy and bronchoalveolar lavage should be performed. These methods are important for diagnosis of tuberculosis, fungal invasion, identification of atypical pathogens, pneumocysta, etc. If neoplastic lung disease, vasculitis, pneumonitis, granulomatosis are suspected it is important to obtain lung tissue sample for histological exanimation. In patients with enlarged mediastinal lymph nodes invasive diagnostic methods should be considered enabling transbronchial biopsy (bronchoscopy, mediastinoscopy, endobronchial ultrasound-guided bronchoscopy) and the further therapy should be modify according to the results. If this diagnostic program does not allow reaching an accurate diagnosis, videothoracoscopy or open lung biopsy should be considered.

Conclusion

Therefore, the diagnostic algorithm in slowly-resolving pneumonia consists of several stages and is aimed at identification of the pathogen causing the pulmonary inflammation and at exclusion of a wide range of diseases mimicking slowly-resolving pneumonia. Despite of new knowledge and new generations of antibacterial drugs slowly-resolving pneumonia has still been a challenging clinical problem that stimulates a physician to continuously improve professional skills.