CASE REPORT

A 56-year-old patient with pigeon breeder’s lung, with fibrosis and sepsis-related cardiogenic shock in the course of fungal-bacterial infection – case report

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is not a single, homogeneous disease, but a complex set of subunits that differ in severity, clinical presentation and natural course. It belongs to a broader group of interstitial lung diseases (ILDs) caused by inflammation and fibrosis occurring in the tissue surrounding the alveoli of the lungs. The distinguishing feature of HP, also called extrinsic allergic alveolitis, is that it is triggered by repeated inhalation of specific organic antigens to which a person is sensitized. The incidence of HP in the UK is estimated at 1 case per 100,000, while in the US that value is between 1.67–2.71 per 100,000 [2]. In Poland, its incidence is estimated at 1.7/100,000 cases [3]. It should be noted that these data may be significantly underestimated, as differential diagnosis of HP is difficult.

HP is a granulomatous interstitial disease that develops in genetically predisposed individuals as a result of an immune response to inhaled antigens. The case is presented of a 56-year-old male with HP with fibrosis, accompanied by severe respiratory failure (requiring HFNOT), significant oedema of the lower extremities, and a large amount of fluid in the right pleural cavity. The patient was initially in circulatory and respiratory failure, requiring infusion of catecholamines. During hospitalization thoracocentesis was performed, complicated by pneumothorax/lung expansion failure. Angio-CT revealed a pulmonary embolism. Targeted antibiotic therapy with voriconazole, meropenem and colistin, as well as bedside rehabilitation, resulted in the stabilization of the patient and improvement of his general condition. The patient was discharged home in a stable condition with the recommendation of home oxygen therapy.

Abstract

Hypersensitivity pneumonitis (HP) is a granulomatous interstitial disease that develops in genetically predisposed individuals as a result of an immune response to inhaled antigens. The case is presented of a 56-year-old male with HP with fibrosis, accompanied by severe respiratory failure (requiring HFNOT), significant oedema of the lower extremities, and a large amount of fluid in the right pleural cavity. The patient was initially in circulatory and respiratory failure, requiring infusion of catecholamines. During hospitalization thoracocentesis was performed, complicated by pneumothorax/lung expansion failure. Angio-CT revealed a pulmonary embolism. Targeted antibiotic therapy with voriconazole, meropenem and colistin, as well as bedside rehabilitation, resulted in the stabilization of the patient and improvement of his general condition. The patient was discharged home in a stable condition with the recommendation of home oxygen therapy.

Key words

fibrosis, environmental factors, respiratory failure, hypersensitivity pneumonitis, pigeon breeder’s lung

Animal and plant origin. Exposure can result from work, hobbies, or the home environment [1, 2]. The current state of knowledge does not allow a clear determination of the cause of the occurrence of the aforementioned immune response in only part of the exposed individuals, but one of the most common hypotheses is the so-called ‘two-hit’ theory, in which multiple exposures to an antigen act as an inducing factor, and genetic factors act as conducive to the onset of the disease [2].

For many years, the clinical course of HP was divided into acute, sub-acute and chronic, depending on the frequency, severity of symptoms (in the acute form – fever, cough and dyspnea resolving spontaneously after cessation of contact with the antigen, less marked in the subacute form, or leading to irreversible changes in the chronic form), intensity of exposure to the antigen, and an arbitrary time interval separating the subtypes. The aforementioned categories suggest a serial evolution of lesions that is not obvious. Moreover, the problem with using the time definition for chronic HP is that it includes cases of chronic pneumonia with, but also without fibrosis. In addition, some patients develop pulmonary fibrosis without prior symptoms that could be attributed to each category, or that would mark the onset of the disease. Accurately distinguishing between acute, sub-acute and chronic conditions is not always possible. Several other classification schemes have been proposed, none of which is fully satisfactory due to the high variability, overlapping clinical images and course of HP. Considering the above, pulmonary societies from the US, Japan and France have divided HP into two main groups: without fibrosis and with pulmonary fibrosis found on imaging or histopathology [4, 5].

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Typical symptoms of HP include progressive dyspnea and non-productive cough, usually resolving when exposure to the causative agent is stopped. Less common are chest tightness and systemic symptoms, such as fever, shivers, weight loss and malaise. Physical examination in HP may reveal the presence of tachypnoea, focal or diffuse crackles, or inspiratory wheezes. At a later stage of the disease, finger clubbing may be present [2].

Diagnosis is based primarily on an accurate and detailed history, taking into account interests and occupational environment to identify the factor that may be causing the symptoms. According to reports, up to 60% of cases fail to identify the causative agent. The main goals of the assessment are to determine potential exposure, classify the severity of respiratory distress and identify characteristic radiological features on high-resolution computed tomography (HRCT) of the chest. In HRCT, the so-called ‘head cheese sign’ consists of healthy lung parenchyma, air traps, ground-glass type lesions and nodular opacities, forming a mosaic-like structure with varying densities on HRCT. As the disease develops, the progression of fibrosis and bronchiectasis can be seen.

Distinguishing HP from usual interstitial pneumonia or non-specific interstitial pneumonia can be very difficult. HP should be suspected in patients with known exposure to an agent causing symptoms, and in patients with radiographic features of interstitial lung disease without specific features suggesting an alternative diagnosis (e.g., sarcoidosis, rheumatic disease, cystic lung disease). Pulmonary function tests usually show restrictive abnormalities with reduced diffusing capacity (DLCO). It is not possible to distinguish between HP with and without fibrosis by using pulmonary function tests, but they are used to monitor disease progression or response to treatment [2].

Broncho-alveolar lavage (BAL) is a useful tool in the diagnosis of HP. Analysis of cellularity in the above examination shows the presence of >30% lymphocytes, with a predominance of T lymphocytes, but not meeting this criterion does not exclude HP and should always be correlated with the clinical and radiological image. In uncertain cases, a lung biopsy is indicated [2].

Tests for specific IgG antibodies directed against potential antigens are available to a limited extent in Poland (only at one research center), but their diagnostic utility is controversial due to the lack of standardization and the occurrence of positive results in exposed individuals without HP and negative results in patients with active disease [6].

**CASE REPORT**

A 56-year-old male was transferred to the Department of Pneumonology of the Military Institute of Medicine – National Research Institute (WIM-PIB) in Warsaw from a regional hospital, where he was hospitalized with significant respiratory failure (SpO2=50% without oxygen supplementation) and cardiogenic shock.

The patient initially presented to the hospital due to rapidly increasing deterioration of exercise tolerance, malaise and the onset of massive oedema of the lower extremities. On admission to hospital, a blood-letting (approximately 1L) was performed due to the detected polycythaemia. In addition, thrombosis of the veins of the right lower limb was detected, and a suspicion of pulmonary embolism was raised based on echocardiography (a CT scan of the pulmonary trunk and thoracic vessels (angio-CT) was waived due to significantly aggravated respiratory failure).

After initial improvement, the patient was discharged home with the recommendation to take low-molecular-weight heparin, followed by dabigatran. Despite the treatment, the patient was re-admitted to the district hospital eight days later due to anuria, recurrence of lower extremity oedema and shortness of breath. During hospitalization, he was diagnosed with acute kidney injury, respiratory failure and circulatory failure requiring the supply of catecholamines.

In view of the exhaustion of diagnostic and therapeutic options, it was decided to transfer the patient to the Department of Pneumonology of WIM-PIB. In 2009, based on the patient’s history, he was diagnosed with hypersensitivity pneumonia (HP), complicated by pulmonary fibrosis, confirmed by a lung biopsy in 2010.

In addition, the patient had a history of anaemia (mild, diagnosed in 2010, with no history of further diagnostics), lower extremity venous thrombosis, and vitiligo. According to the patient, there was no exacerbation of disease symptoms between the biopsy and the current hospitalization. On further history taking, the patient mentioned that in his spare time he raises pigeons.

At the time of admission to the Department of Pneumonology, the patient remained in a very severe general condition, awake, alert, and oriented with symptoms of cardiogenic shock and respiratory failure. Basic laboratory and imaging diagnostics were performed. Additional tests revealed significant findings: NTproBNP 7186.0 pg/mL (N: 0–194.0), CRP 12.7 mg/dL (N: 0–8.0), PCT 0.68 ng/mL (N: 0–0.8), WBC 16.60 x 10⁹/l (N: 4.30–9.64) with neutrophil smear, haematuria, leukocyturia, hypoalbuminaemia (1.9 g/dL; N: 3.9–4.9), troponin 67.9 ng/L (N: 0–14). An intra-arterial catheter was inserted, and arterial blood gasometry was taken, which showed: pH 7.457 (N: 7.35–7.45), pCO2 39.3 mmHg (N: 35.0–48.0), pO2 56.5 mmHg (N: 83.0–108.0). Blood, sputum and urine samples were collected for microbiological examination.

Empiric antibiotic therapy (pipercillin/tazobactam, amikacin) and infusion of unfractionated heparin with flow modified according to APTT were implemented. An infusion of norepinephrine and dobutamine was maintained under blood pressure control. The ECG showed sinus tachycardia with a heart rate of 114/min and right bundle branch block, as well as manifestations of right ventricular overload. Bedside cardiac echocardiography (Echo) showed significantly enlarged right heart chamber and a mildly enlarged left atrium. Left ventricular dimensions were normal. Features of right ventricular overload with hyperkinesis of its free wall, extensive left ventricular wall segmental wall motion abnormalities, apical akinesis, akinesis of the distal half of the lateral, posterior and anterior walls, and proximal half of the inferior wall, with apparent myocardial reduction in the lateral and posterior walls, were seen. In addition, Echo showed a left ventricular ejection fraction of about 35%. In the area without myocardial damage, the left ventricular muscle showed features of hypertrophy. Significant tricuspid regurgitation (TRPG=78mmHg, Vmax=4.14m/s) and a wide pulmonary trunk were found, with a shortened Acct=57ms. The inferior vena cava remained undilated.

A bedside chest X-ray (Fig. 1) in the sitting position showed a large amount of fluid in the right pleural cavity – up to...
A 56-year-old patient with pigeon breeder’s lung, with fibrosis and sepsis-related cardiogenic... the level of the IV-V rib in the axillary line, reticulonodular opacities in the visualized pulmonary parenchyma in the upper field of the right lung (RL), and interstitial lesions in the lower and middle fields of the left lung (LL). In addition, the examination showed an enlarged cardiac silhouette, the mediastinum shifted to the left side. The left pleural cavity remained free of fluid. Moreover, features of chronic congestion in the pulmonary circulation were found. Angio-CT was not performed at this stage due to the patient’s severe respiratory failure and the lack of a safe option to transport the patient to the radiology imaging room (the patient did not consent to intubation and mechanical ventilation). After initial treatment, cardiovascular stabilization was achieved and pressure amines were discontinued. After the result of microbiological culture of sputum, which showed Escherichia coli and Klebsiella pneumoniae, antibiotic therapy was adjusted to targeted (amikacin, meropenem).

In order to evacuate the fluid accumulated in the right pleural cavity, it was decided to perform thoracocentesis. As a result of the procedure, 1,200 ml of serous fluid was evacuated, and partial expansion of the lung was achieved. On auscultatory physical examination, a quiet breath sound was heard on the right side. A follow-up chest X-ray revealed a likely iatrogenic right-sided pneumothorax with fluid (Fig. 2), for which a suction drain was placed into the right pleural cavity. A few hours after insertion of the drain, the patient developed symptoms of circulatory failure. Blood pressure measurement showed hypotension (60/30 mmHg) – norepinephrine infusion was implemented again. The culture of pleural fluid performed showed mould fungi – Aspergillus fumigatus. Targeted treatment with voriconazole was implemented. The patient was repeatedly asked for consent for intubation and the implementation of mechanical ventilation due to significant respiratory failure – he refused, despite being informed of the direct threat to health and life without the implementation of this therapy.

In the control microbiological examination of the pleural cavity fluid and urine samples, Acinetobacter baumanii MDR and Klebsiella pneumoniae ESBL+ were sequentially isolated, and antibiotic therapy with colistin and meropenem was implemented.

After the patient’s clinical condition stabilized, the radiological diagnostics were deepened. An angio-CT scan visualized a dilated pulmonary trunk (37 mm) and a intraluminal contrast filling defect in the segmental artery in segment 9 of the left lung and segment 5 of the right lung, indicating pulmonary embolism, as well as opacification distal to the involved arteries (Fig. 3). The examination also showed features of fibrosis at the basal part of both lungs, increased emphysema and the presence of a large amount of fluid in the right pleural cavity (Fig. 4). In addition, the angio-CT detected atelectatic-inflammatory opacifications over the fluid in RL. An enlarged cardiac silhouette with a trace of fluid in the pericardial sac was observed.

Throughout his hospitalization the patient remained monitored in the intensive pulmonary care room. In the following days of his stay, the patient stabilized circulatory (the infusion of pressor amines was discontinued) and remained awake, alert and oriented, but with severe respiratory failure. Saturation measurements indicated values reaching a maximum of 83% during high-flow nasal oxygen therapy (HFNOT), with a flow rate of 60 L/min, with an oxygen...
with rivaroxaban 20 mg/day was implemented. Follow-up examinations were scheduled for re-qualification for lung transplantation.

A follow-up of the patient’s condition 17 months after the end of hospitalization showed a resting saturation of 92–94% without oxygen supplementation, which decreased to 75% during significant exercise. In addition, lung expansion occurred and the pleural drain was removed. Three months after the hospitalization, the patient was put on the transplant list. While he is still awaiting surgery, his overall performance is satisfactory, with a WHO score of 0/1. The patient is using oxygen therapy at night. Polycythemia persists in blood tests. It was recommended to increase the time of oxygen therapy to a minimum of 16 hours per day.

**DISCUSSION**

HP mainly affects non-smoking middle-aged men, which is consistent with the case described above. In addition, the antigen triggering the patient’s immune response was most likely avian proteins, which is also characteristic (the so-called “bird breeder’s lung”). Even negligible contact with bird faeces triggered an increase in his symptoms. Cigarette smoking is associated with a reduced risk of HP, but smokers with HP have been observed to have a higher mortality rate and a more severe course of the disease [7, 8].

The treatment of HP presents many difficulties due to the lack of a standardized management algorithm. The gold standard in the treatment of this disease is avoidance of harmful antigens and treatment with prednisolone [5]. Isolating patients from the harmful effects of avian antigens can be something of a challenge. Allergenic avian proteins can be present in the environment for extended periods of time, despite the early clean-up of animal tracks [9]. In addition, up to 60% of HP patients fail to identify the causative agent [2]. Another important aspect of management is that HP patients with fibrosis require different treatment from those without fibrosis. A cohort study involving 202 patients, showed the efficacy of avoiding harmful antigens and prednisolone supply in the group without fibrosis, while patients with fibrosis had a poor prognosis and no therapeutic effect of corticosteroid treatment [5, 10].

In the early phase of treatment of the patient in the presented case report, diagnosed with HP with fibrosis and severe respiratory failure, the treatment with glucocorticosteroids (GCS) was introduced due to their anti-inflammatory effects. After the patient’s general condition stabilized, two attempts were made to discontinue the drugs. Both led to an exacerbation of symptoms and exacerbation of respiratory failure, resulting in the need to continue therapy, despite the advanced and established fibrosis process.

The hope for effective therapy stems from the use of immunosuppressive drugs, such as mycophenolate mofetil and azathioprine, which improve and stabilize parameters in pulmonary function tests in patients with chronic HP. An additional advantage is that their administration makes it possible to reduce the dose of GCSs, and thus also reduce the risk of side-effects due to their use [11, 12]. Reliable studies on patients with the fibrotic presentation are unfortunately lacking. An alternative for patients with chronic HP who have not responded positively to allergen avoidance and GCS therapy is rituximab [13]. However, the aforementioned concentration in the breathing mixture estimated at 91%. Targeted antibiotic therapy with voriconazole, meropenem and colistin was continued. The leakage in the right pleural cavity drainage persisted, with the drain receiving purulent and bloody fluid. Physical examination revealed rales and wheezing over the entire right lung. A follow-up chest X-ray showed resolution of the pneumothorax at the base of the right lung. After attempting to clamp the drain, the X-ray showed a progression of the pneumothorax from 28 mm to 35 mm in one day. Accordingly, the clamp was released again. Suction drainage was continued. Due to the result of the pleural fluid culture in which A. baumann MDRI was again isolated, amikacin was included in the treatment, based on the antibiogram. Bedside rehabilitation was started.

In view of the exhaustion of therapeutic options, the lack of expected improvement despite intensive treatment, and in view of the irreversibility of the consequences of the course of the disease, an enquiry was sent to the transplant centre about the possibility of qualifying the patient for lung transplantation. A negative opinion was obtained due to active fungal and bacterial infection of the lungs.

Due to persistent leakage from the pleural drainage and the lack of further lung expansion, it was decided to terminate the suction drainage and apply a Heimlich flutter valve.

As a result of the ongoing rehabilitation, physical performance improved. Oxygen flow was reduced to 6–8 L/min via intranasal cannulas. The arterial blood critical parameters analyzer showed pH 7.45 (7.35–7.45); pO2 56.8 mmHg (83.0–108.0); pCO2 38 mmHg (35.0–48.0). After 87 days of hospitalization, the patient was discharged home with recommendations for home oxygen therapy via intranasal cannulas using two concentrators (connected in parallel by a Y-connector), with a flow rate on each device of 3–4 L/min (resulting in a total flow rate of 6–8 L/min). Continued exercise rehabilitation was recommended, with the use of a Venturi oxygen mask with reservoir. Due to the pulmonary embolism and the high risk of its recurrence, oral anticoagulation...
treatment options were limited, due to the active bacterial and fungal inflammatory process. Nintedanib has also been shown to be effective against placebo in patients with progressive ILD with fibrosis, among whom 26.1% were HP patients [14].

According to the literature, HP with fibrosis is accompanied by a significant risk of venous thrombosis and pulmonary embolism [15]. The presented patient’s clinical presentation supported the diagnosis of pulmonary embolism, the origin of which was most likely venous thrombosis of the lower extremities. In order to confirm this disease entity, it was necessary to perform angio-CT in the patient. However, the examination was initially not performed due to the patient’s circulatory failure and severe respiratory failure, and the inability to safely transport the patient to the radiology imaging room (the patient did not consent to intubation and mechanical ventilation). The patient’s oxygen requirement was more than 60L/min, which could not be achieved with passive oxygen therapy in a mobile setting. Transport without adequate oxygen therapy was burdened with significant risk of sudden cardiac arrest. In the absence of the possibility of confirming pulmonary embolism with imaging studies and after stabilization of the cardiovascular system with norepinephrine and dobutamine infusions, the decision was made to administer unfractionated heparin until angio-CT was performed. A further radiological examination of the patient showed an image that was typical of pulmonary embolism.

The initially very severe condition of the patient also included cardiogenic shock. The presence of massive peripheral oedema, as well as hypotension requiring continuous infusions of norepinephrine and dobutamine, the presence of a large amount of fluid in the pleural cavity, and finally, the echo-cardiographic features of right ventricular overload and observed reduction in ejection fraction, translated into the observed clinical image. Such abnormalities could have resulted from exacerbation of congestive heart failure, co-existing septic shock, and also (particularly right ventricular overload) from concomitant pulmonary embolism and pulmonary hypertension which, in long-term HP with fibrosis, can develop over time [2]. All these factors translated into poor prognosis for the patient and significantly affected the therapeutic process. During further treatment with antibiotics, diuretics (with maintenance of a negative fluid balance) and by optimizing the treatment of heart failure, cardiovascular stabilization and a significant reduction in oedema were achieved. It was possible to discontinue catecholamines due to stabilization of blood pressure values.

Due to the high concentration of inflammatory factors in the blood and a significant amount of fluid in the right pleural cavity, thoracocentesis was performed, removing the fluid for microbiological examination. The results of the examination revealed the presence of *Aspergillus fumigatus* fungi and *Acinetobacter baumannii* MDR. Examination of a urine sample showed the presence of *Klebsiella pneumoniae* ESBL+ bacteria. Treatment was therefore started according to the antibiogram with voriconazole, colistin and meropenem.

Another challenge in the treatment of the described patient was the failure to expand the lung and thus improve ventilation, despite the use of interventions to evacuate fluid from the pleural cavity. The most likely causes of this condition were chronic fibrosis of the lung parenchyma and ongoing active fungal and bacterial infection. The duration of fluid-induced atelectasis before the first hospitalization was unknown. It is highly likely that the compression of the lung by the fluid in the pleural cavity had been going on for a long time before the patient was admitted to the hospital, as indicated by his adaptation to hypoxemic conditions. Due to persistent leakage and the need to continue antifungal therapy with voriconazole, a Heimlich flutter valve was used with the recommendation of removing the drain at the end of treatment. According to the literature, the use of such a solution may contribute to reducing additional hospital interventions, patient suffering, and improvement of their comfort, with similar results, compared to more invasive interventions [16].

Due to the exhaustion of available therapeutic methods and the lack of expected improvement in the patient’s condition, despite intensive therapy, his eligibility for lung transplantation was initiated. This operation significantly improves the prognosis of patients with HP. Among 114 HP patients who underwent the transplantation procedure, one, three and five-year survival rates were 85%, 75% and 70%, respectively [17]. However, the transplant centre gave a negative opinion due to the active infection. Guidelines from the International Society for Heart and Lung Transplantation recommend that patients with interstitial lung disease should be referred for lung transplant qualification early in their disease to maximize their chance of being listed for transplant [18]. Non-pharmacological interventions, such as pulmonary rehabilitation, are also recommended as an important part of the comprehensive treatment of patients with progressive interstitial lung disease [5, 18].

It is worth noting that as a result of rehabilitation and treatment of the active infection with meropenem, colistin and voriconazole, a significant improvement in cardiovascular stabilization, inflammatory parameters and physical performance was observed in the described patient. After almost three months, he was discharged home with the recommendation to administer oxygen therapy using an intranasal cannula while using two oxygen concentrators connected in parallel via a Y-connector. An oxygen flow rate of 3-4 L/min on each device was recommended, which when added together gave a total flow of 6-8 L/min. It should be noted that the maximum flow of one concentrator was 5 L/min, but due to the chronic condition of the patient, who required 6 to 8 L/min, and the risk of damage to the concentrator at its maximum output, it was decided to use two devices, connected in this way. Guidelines published by the American Thoracic Society recommend long-term ambulatory oxygen therapy in patients with interstitial lung disease and severe chronic resting hypoxemia [19]. Patients and their caregivers should receive training on the use of home oxygen therapy to ensure patient safety.

Despite his initial critical condition, long hospitalization and the presence of complications, by the 17-month follow-up the patient’s functions had returned to a satisfactory level, with at rest, his respiratory function preserved. All of this contributed to significant improvement in his independence and quality of life until such time when he could receive a transplant.
CONCLUSIONS

Patients with HP have a different disease course depending on the form of the disease. In HP patients with pulmonary fibrosis, isolation from potential triggers, chronic oxygen therapy in case of respiratory failure and adequate thromboprophylaxis are important aspects. If the disease progresses in patients with this condition, it is important to consider lung transplantation to increase survival, particularly in the face of progressive pulmonary fibrosis.

REFERENCES