OPIS PRZYPADKU CASE REPORT

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Goodpasture's syndrome in the course of H1N1 influenza A – case report

Zespół Goodpasture'a w przebiegu grypy A/H1N1 – opis przypadku

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Słowa kluczowe
grypa A/H1N1, zespół Goodpasture'a, zakażenie grzybicze

Summary

Introduction. Coexistence of glomerulonephritis with pulmonary hemorrhage was described for the first time as Goodpasture's syndrome in 1957. Several years later characteristic changes in pulmonary and renal vessels as well as antibodies against glomerular basement membrane (anti-GBM) were described. Etiology of the syndrome remains unknown. According to one hypothesis the syndrome is associated with influenza virus infection.

Case report. We present a case study of 53-year-old patient with negative past medical history who was admitted to the ICU due to the fulminant course of respiratory failure. At the admission to the hospital patient received one dose of oseltamivir (H1N1 influenza epidemy). Chest radiography revealed interstitial pneumonia. PCR results confirmed A/H1N1 influenza virus infection. Bronchofiberoscopy revealed alveolar hemorrhage, confirmed by chest computed tomography. In the fifth day of oseltamivir treatment no evidence of the A/H1N1 virus in bronchoalveolar lavage was found. Positive results of immunological examinations allowed to diagnose Goodpasture's syndrome. Methylprednisolon pulses, plasmapheresis and courses of cyclophosphamide were applied. Treatment led to the reduction of anti-GBM antibody titer. Prolonged therapy with associated risk factors and decrease in patient's immunological status were the main causes of sepsis and septic shock. Despite the causal treatment the patient died.

Conclusions. Viral infection can induce adverse events as a result of excessive production of antibodies and uncontrolled cell response. Immunodeficiency was the most important risk factor of infection in presented case.

Streszczenie

Wstęp. Zmiany o charakterze *glomerulonephritis* występujące z krwotokiem płucnym po raz pierwszy nazwano zespołem Goodpasture'a w 1957 roku. Kilkanaście lat później wykazano obecność zmian w płucnych i nerkowych naczyniach, a także przeciwciała przeciwko błonie podstawnej naczyń nerkowych. Etiologia zespołu jest nieznana. Jedna z hipotez łączy występowanie zespołu z zakażeniem wirusem grypy.

Opis przypadku. Opisujemy przypadek 53-letniego pacjenta bez przeszłości chorobowej, którego przyjęto do OIT z piorunującego przebiegu niewydolności oddechowej. Obraz rtg klatki piersiowej odpowiadał śródmiąższowemu zapaleniu płuc. W dniu przyjęcia pacjent zażył jedną tabletkę oseltamiwiru (epidemia grypy A/H1N1). Badanie PCR potwierdziło zakażenie wirusem grypy A/H1N1. W badaniach bronchoskopowych stwierdzono krwawienie pęcherzykowe, uzyskując potwierdzenie w CT klatki piersiowej. W materiale z płukania pęcherzykowo-oskrzelowego w 5. dobie leczenia oseltamiwirem nie stwierdzono obecności wirusa A/H1N1. Przeprowadzona diagnostyka immunologiczna upoważniła

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do rozpoznania zespołu Goodpasture'a. Włączono sterydoterapię, wykonano cykl plazmaferez, stosowano pulsy metyloprednizolonu oraz kursy cyklofosfamidu. Zastosowane leczenie obniżyło miano p/ciał anty-GBM. Długotrwała terapia i związane z nią czynniki ryzyka oraz spadek odporności pacjenta były bezpośrednią przyczyną sepsy i rozwijającego się wstrząsu septycznego. Pomimo leczenia przyczynowego pacjent zmarł.

Wnioski. Infekcja wirusowa jest mechanizmem indukującym niekorzystne zjawiska spowodowane produkcją przeciwciał oraz nadmierną niekontrolowaną odpowiedzią komórkową. Zaburzenia w układzie immunologicznym są w tym wypadku najważniejszym czynnikiem ryzyka zakażenia.

INTRODUCTION

In 1919, Ernest Goodpasture described two cases of pneumonia of unknown aetiology. Both were related to influenza and both resulted in the patient's death. Pulmonary haemorrhage and signs of renal failure were present in both cases. No microorganisms were found that could be the cause of such a dramatic course of the disease. Initially, it was suspected that both cases had been caused by an unknown virus. Autopsies revealed alveolar haemorrhage and hyaline membrane formation in the lungs. Haemorrhages were also found in the renal cortex (1).

The name "Goodpasture syndrome" was first used in 1957, by two Australian researchers who described 9 cases of glomerulonephritis with pulmonary haemorrhage (2, 3). Presence of lesions in pulmonary and renal vessels had not been revealed before 1965, when the immunofluorescence technique was applied. Two years later, presence of anti-GBM antibodies (anti-glomerular basement membrane antibodies) was revealed (3, 4). Since 1971, the nosological entity that is characterised by vasculitis with the presence of anti-GBM antibodies has been referred to as the Goodpasture syndrome (2, 3). Although the aetiology of Goodpasture syndrome currently remains unknown, several hypotheses about its cause have been formulated. One of these hypotheses draws a connection between occurrence of the syndrome and viral infections, mostly involving the influenza virus (5).

CASE STUDY

53-year-old patient with no relevant history of diseases, admitted to hospital due to a fever of over 38°C that persisted for two days, dry cough, and increasing shortness of breath at rest. Chest radiography revealed extensive stitial consolidations, granular, non-overlapping consolidations, which might have been indicative of interstitial lesions. No lesions typical of congestive heart failure were found. On the day of admission, the patient received a single, 75 mg oseltamivir dose (this was the period of the A/H1N1 influenza epidemic). Physical examination did not reveal crackles at the base of the lung. The patient's dyspnoea exacerbated within the next several hours. As the patient's respiratory failure was progressing, he was moved to the Intensive Care Unit. Given his increasingly laboured breathing, the patient was intubated and connected to a mechanical ventilator with the following parameters: SIMV, $Fi0_2$ 1.0 (100% of oxygen provided by the ventilator), and PEEP 10 cm H_20. Remifentanil and pressor amines were administered in order to maintain perfusion pressure. Due to suspected influenza A(H1N1) virus infection, a throat swab sample was collected and oseltamivir dosage was increased to 2 x 150 mg. Table 1 lists the virusological and bacteriological diagnostics carried out in the course of treatment, along with the results. An echocardiogram revealed pulmonary hypertension (PASP 53 mmHg) and normal heart chamber size, with no hypertrophy or impaired contractility. As increasing pressor amine doses had to be administered in order to maintain blood pressure, the decision was made to introduce steroids, pursuant to septic shock treatment guidelines (steroids administered at the rate of 10 mg/h). The result was a prompt and clear improvement in blood oxygenation. After approx 4 hours of steroid infusion, a clear improvement in ABG parameters could be observed, which continued in the subsequent tests – pO_2 (arterial oxygen pressure): 148 mmHg, pCO_2 (arterial carbon dioxide pressure): 43 mmHg. $Fi0_2$ values decreased gradually. 6 hours after steroid therapy was commenced, the patient's respiratory parameters were as follows: venous saturation: 78%, oxygen index: 21, Murray lung injury score: 2.5 (which confirmed Acute Respiratory Distress Syndrome – ARDS), pO_2/FiO_2: 238, pulmonary compliance: 19 ml/cm H_2O. An initial bronchofiberoscopic examination revealed bloody secretions from the lower left bronchus. Subsequent bronchofiberoscopies revealed alveolar haemorrhage. The result was a haemoglobin level decrease from 12 g/dl do 9.12 g/dl. Immunological examinations were carried out in order to rule out an immunological syndrome or disease. At the same time, bronchoalveolar lavage samples collected on the fifth day of oseltamivir treatment contained no evidence of A/H1N1 virus. A summary of immunological examinations can be found in table 2. Both creatinine levels (1.1 mg/dl) and glomerular filtration rate (102 ml/mim) were normal. However, urinalysis revealed microhaematuria (20-30 erythrocytes in the visual field).

A gradual improvement of the patient's general condition could be observed, as indicated by improved respiratory function. $Fi0_2$ was decreased to 0.4, however PEEP could not be reduced successfully. CRP concentration remained high (124 mg/dl). The particularly high anti-GBM antibody titer of 320 IU legitimised the diagnosis of Goodpasture syndrome. However, no anti-alveolar basement membrane antibodies were found. This had been the only evidence of this rare disease available at that stage of diagnostics and treatment. Steroid dose was increased to 1g of prednisolon on

Table 1. Virusological and bacteriological examinations (in order of execution).

No.	Test type	Result
1	A/H1N1 influenza	positive – RNA detected
2	CMV - DNA	negative
3	EBV - DNA	negative
4	RSV - RNA	negative
5	*Mycoplasma pneumoniae*	negative
6	*Legionella pneumophilia*	negative
7	A/H1N1 influenza	negative
8	*Chlamydophila pneumoniae*	negative
9	Mycobacterium tuberculosis complex	negative
10	Anaerobic and aerobic bacteria blood cultures	negative
11	BAL cultures for anaerobic and aerobic bacteria	negative

Table 2. Immune tests (in order of execution).

No.	Antibody type	Result
1	Anti-pANCA, cANCA neutrophil cytoplasmic antigen	not detected
2	Anti-alveolar basement membrane	not detected
3	Anti-glomerular basement membrane	320 titer detected
4	Anti-myositis antigen	not detected
5	ANA3	not detected
6	AMA, type M2	not detected
7	ASMA	not detected
8	ANA2	not detected
9	Anti-glomerular basement membrane (repeated testing)	640 titer detected

alternating days. An x-rat CT scan showed extensive opacity in the acini – dense fluid in the alveoli (48 HU) – blood (fig. 1A, 1B, 2). As the anti-GBM antibody titer was rising (640) despite steroid doses having been increased from the 4th day on, plasmapheresis was carried out (14 instances of this procedure were carried out in total throughout therapy). Pulsed doses of methylprednisolone (1 mg) were administered on alternating days – 14 doses total. The high anti-GBM antibody titer with simultaneous absence of ANCA antibodies allowed to introduce cyclophosphamide courses to the therapy. A temporary improvement was achieved, as indicated by decreased alveolar bleeding. Respiratory parameters improved (confirmed by an ABG test), which made it possible to discontinue mechanical ventilation and to extubate the patient. In the subsequent days, CRP levels had grown from 88 mg/dl to 374 mg/dl indicating inflammation. As an inflammation of fungal aetiology was suspected, antigen marker and antibody tests were carried out. Together with the clinical picture of the disease, increased anti-*Aspergillus* and anti-*Candida* antibody concentration provided a rationale for capsofungin treatment. Antigen marker tests proved negative, as was the case with blood cultures. The patient received an immunoglobulin drip for three consecutive days. Anti-GBM antibody concentration was tested throughout therapy, the result being an initial decrease in titer, followed by a subsequent increase. Monoclonal protein test yielded a negative result. The patient was reintubated and mechanical ventilation was reintroduced due to the severe deterioration of the patient's general condition. Dialysis treatment was commenced due to anuria, distorted water and electrolyte balance, and distorted acid-base homeostasis. Despite intensive treatment, the patient's condition continued to deteriorate in the subsequent days, and coagulopathy in the form of DIC occurred (this happened in the terminal stage of the disease, concurrently with signs of septic shock). The septic shock caused a multi-organ failure that resulted in the patient's death.

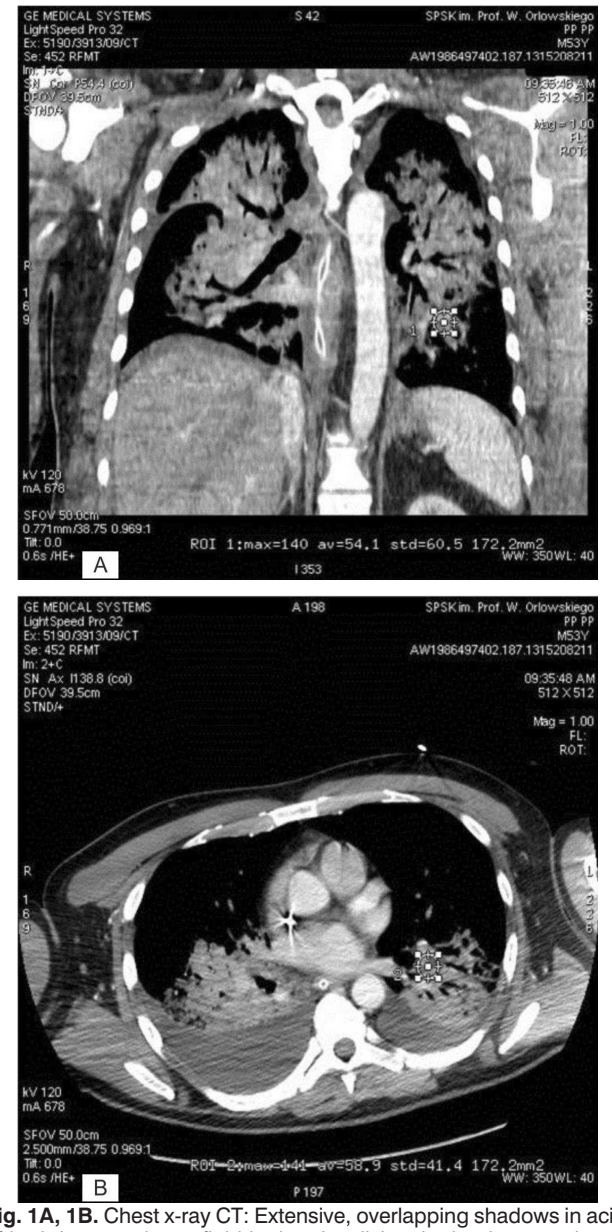

Fig. 1A, 1B. Chest x-ray CT: Extensive, overlapping shadows in acini of both lungs – dense fluid in the alveoli (marked points – 1,2) – 48 HU – blood-air bronchogram visible, fine peribronchial nodules present particularly in the bottom section of the lungs, small amount of fluid in both pleural cavities (14 HU); three paratracheal lymph nodes on the right up to 20 cm, with blistering.

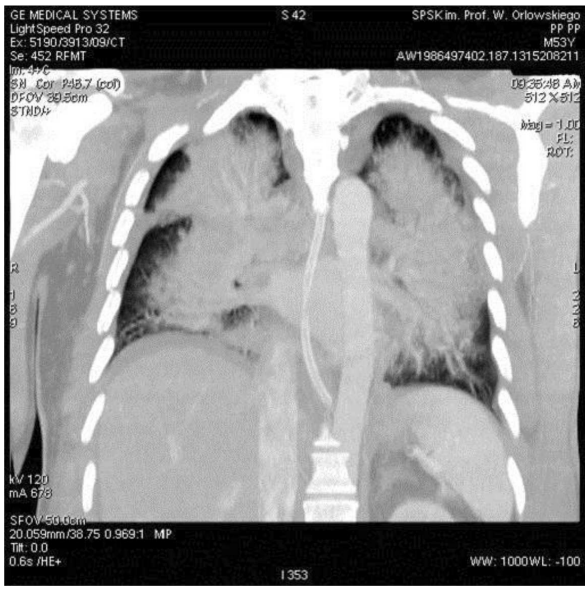

Fig. 2. Chest x-ray CT – ARDS.

DISCUSSION

A typical characteristic of Goodpasture syndrome is the presence of glomerulonephritis and, variably, haemorrhagic lesions in the lungs (6). Goodpasture syndrome is classified as an autoimmune disease. The main effect of this disease is the destruction of the basement membrane of glomerular capillaries and alveoli in the mechanism of an immune complex that is formed during the activation of the complex system. The cause of this disease is IgG immunoglobulin adverse to the terminal domain of type IV collagen fibres (antigen). The result of the complex's activity is the formation of a focal necrosis which manifests itself in progressive organ failure. Goodpasture syndrome is a relatively rare nosological entity. The disease is more frequently found in white males of approx. 40 years of age. The reason why secretion of IgG class antibodies takes place remains unknown. Potential risk factors include smoking, upper respiratory tract infections, genetic predisposition, or exposure to hydrocarbons (7). Approximately 40% of patients experience upper respiratory tract infection symptoms such as fever, cough, dyspnoea, or flu-like symptoms. However, the prevailing sign of the Syndrome is haemoptysis, occurring in 65% of patients. The first group of signs that Goodpasture described occurred in six weeks following infection with the influenza virus (1). In 1972, Wilson et al. described a case of Goodpasture syndrome in a young woman, with the typical signs and chest radiography results (5). Microbiological and virusological diagnosis pointed to influenza A2 virus infection as the cause of the disease. According to the authors, the connection with influenza was confirmed by the 16-fold increase in anti-influenza antibody titer on the ninth day of the disease. However, antibody concentration decreased almost tenfold throughout the subsequent two weeks. The half-life of IqG class antibodies amounts to 14 days, therefore, the above-mentioned connection to the influenza virus is disputable (8).

In the presented clinical case, Goodpasture syndrome was diagnosed during an influenza A(H1N1) epidemic. Influenza is the most commonly-occurring disease in the world, and it's characterised by a very high incidence, with a peak period between autumn and spring. As the patient showed signs typical of influenza, therefore treatment was commenced pursuant to the guidelines for dealing with such infections, and test samples were collected. Presence of the virus was detected with PCR (polymerase chain reaction), a specific and highly sensitive method that allows detecting even a single ribonucleic acid particle (9). The oseltamivir treatment that had been introduced before the diagnosis was made failed to decrease the number of copies of the virus to an untraceable threshold (there was evidence of influenza AH1N1 virus in the collected samples). A subsequent test, carried 5 days after the oseltamivir dose had been doubled, revealed no presence of the virus. The increase of the oseltamivir dose to 300mg was in line with WHO guidelines (9-12). Haemoptysis and signs of progressing respiratory failure justified suspicions of alveolar haemorrhage. In such turn of events, the key diagnostic element is a bronchofiberoscopic examination with bronchoalveolar lavage. At the same time, serological tests need to be performed in order to establish what caused the syndrome. Repeated bronchofiberoscopic examinations, which revealed more bloody secretions during the bronchoalveolar lavage (which indicates that there could have been no bleeding from iatrogenic lesions), as well as specific behaviour of the BAL fluid (subsequent portions of fluid were increasingly bloody) led us to believe that alveolar haemorrhage was the most likely diagnosis. Alveolar haemorrhage was confirmed by a cytological test (count of alveolar macrophages with haemoglobin content – Goude Score). At the same time, a wide-spectrum serological test was performed in order to establish the aetiology of the alveolar haemorrhage (tab. 2). Repeated serological tests ruled out, among others, the following: Wegener's granulomatosis, vasculitis, Churg-Strauss syndrome, drug-induced syndromes, muscle inflammation, lupus erythematosus, and antiphospholipid syndrome. Given the very high anti-basement membrane antibody titer, Goodpasture syndrome seemed to be the most likely diagnosis.

The signs that accompany Goodpasture syndrome are usually specific. Glomeruli are affected in all cases. Anti-GBM antibodies are found in the serum in more than 90% cases. Furthermore, only 2% of patients show signs of alveolar damage with no signs of renal failure (13). In such cases renal biopsy provides the final answer. Renal damage is also known to occur with no necrotic lesions in the lungs. Alveolar haemorrhage is not, therefore, specific to all cases of Goodpasture syndrome. As regards patients in whom no anti-alveolar basement membrane antibodies are detected, some authors recommend lung biopsy (13). Although anti-GBM

antibodies were detected in the discussed case, no anti-alveolar basement membrane antibodies were found. Given the patient's severe condition and the confirmed diagnosis, a biopsy would have only posed additional threat of pulmonary haemorrhage. Most of all, the patient's clinical condition called for treatment of the acute respiratory failure. The treatment applied, consisting of methylprednisolone, cyclophosphamide, and a series of plasmapheresis decreased the antibody concentration, stopped the pulmonary haemorrhage, and improved the patient's clinical condition. Comprehensive treatment presents an opportunity to stop the progressing renal failure that accompanies this illness. Furthermore, many researchers confirmed the beneficial effect of plasmapheresis (14-17).

Patients who did not require renal replacement therapy during treatment were much more likely to regain normal renal function than patients who had to undergo dialysis therapy. Treatment should continue until double negativation of anti-GBM antibody titer occurs. Unfortunately, use of invasive diagnostic and therapeutic procedures and prolonged treatment in the ICU are re-infection risk factors. Immunosuppressive therapy, regardless of the method in question, is considered the primary fungal infection risk factor, with venous catheters being the second-biggest fungal infection risk factor. Apart from facilitating administering the right therapy, large-diameter catheters create the conditions for a canal to form at the introduction site. Catheter care is another, independent risk factor. **All blood culture tests proved negative in the described case, though this does not rule out fungal infection (the percentage of positive blood cultures in the case of invasive fungal infections amounts to 20).** The administered echinocandin therapy is an elective therapy in the case of *Candida* infections. Capsofunging, which was used to supplement the therapy, is known to show *in vitro* activity against *Aspergillus* strains (18). Anti-*Aspergillus* antibodies can be found in healthy people, therefore an infection of this sort seems unlikely. The patient has died of invasive fungal infection, which has probably occurred as a complication following immunosuppressive therapy.

Goodpasture syndrome occurs with a frequency of 1 case per million per year (19). Final stage survivability rate in treated patients fluctuates between 60 and 90%. Relapses are known to occur in the course of the syndrome. There are cases in literature of a triple relapse with a severe clinical condition (19). Pulmonary haemorrhages occurring after acute infections of the upper respiratory tract are the key life-threatening factor.

CONCLUSIONS

1. Every infection that does not respond to treatment and causes acute respiratory failure over a short period of time should raise suspicions of an autoimmune disease.
2. Viral infections are a mechanism that induces adverse phenomena triggered by antibody production and excessive, uncontrolled cellular response. They might induce adverse phenomena that lead to excessive production of antibodies attacking the system's own cells and tissues.
3. Immune system disorders are a highly-important factor in reinfection.

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