

Fatal pulmonary complication during induction therapy in a patient with ANCA-associated vasculitis

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ANCA-associated vasculitis (AAV) is an inflammatory systemic disorder affecting small to medium sized vessels and likely leading to any organ dysfunction. Adequate treatment is important to avoid mortality or severe organ damage. In most cases initial treatment (induction therapy) allows to achieve remission. Induction therapy leads to immunosuppression and may cause severe infections. However, in vasculitis patients even an intensive immunosuppressive therapy is rarely complicated by an invasive fungal infection.

We present a case in a 29-year old male patient with newly diagnosed AAV. He suffered a fatal pulmonary complication of the induction immunosuppressive treatment. Pathological (infectious) changes in the lungs were misinterpreted as progression of the vasculitis and he died due to disseminated angioinvasive aspergillosis. A clinical course, imaging and histopathology of this case are described and discussed.

Keywords: ANCA-associated vasculitis, immunosuppressive therapy, invasive aspergillosis

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INTRODUCTION

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an inflammatory systemic disorder characterized by the production of ANCA (1). Immunosuppressive agents are the mainstay of treatment, divided into a remission induction and a maintenance therapy. Glucocorticoids with cyclophosphamide remain the standard care in consensus guidelines for the treatment of generalised disease. However, even with the best available therapy, relapse rates remain unacceptably high and treatment-related morbidity and mortality remain high as well (2–4).

Both vasculitis itself and complications of induction therapy may cause death (5). However, in vasculitis patients even an intensive immunosuppressive therapy is rarely complicated by an invasive fungal infection (6). In this article we present a case of AAV resulting in death, due to angioinvasive pulmonary *Aspergillus* infection.

CASE REPORT

A 29-year old male patient was admitted to the hospital with complaints of a cough, urine discolouration and a decreased urine output. On clinical examination, the patient presented afebrile, with a blood pressure of 170/80 mmHg and a heart rate of 80 bpm. Bilateral moist rales were observed on lung auscultation. During the examination, the patient coughed up blood for the first time. Laboratory studies demonstrated leukocytosis ($12.7 \times 10^9/L$), eosinophilia ($2.1 \times 10^9/L$), high ratio of the erythrocyte sedimentation rate (66 mm/h), plasma C-reactive protein (30 mg/L) and myoglobin (505 $\mu g/L$). His creatinine (238 $\mu mol/L$) and urea (12 mmol/L) levels were markedly elevated. The urine analysis showed proteinuria and hematuria. Tests for blood, urine cultures, and infectious diseases (tuberculosis, hepatitis B and C, HIV) were all negative. An abdomen ultrasound revealed diffuse changes of the renal parenchyma. An initial chest X-ray showed polysegmental infiltration in the both lungs, which resolved after treatment with amoxicillin/clavulanic acid.

Considering a systematic disease, an autoantibody analysis was obtained and a test for ANCA (c-ANCA pattern) was positive. A kidney biopsy was consistent with an active ANCA-associated crescentic focal necrotizing glomerulonephritis

without immunoreactive deposits (Fig. 1). During the first week of hospitalization the patient's renal function decreased rapidly (urea 36 mmol/L and creatinine 807 $\mu mol/L$). A treatment with high-dose glucocorticoids and intravenous cyclophosphamide (500 mg/m²) was initiated.

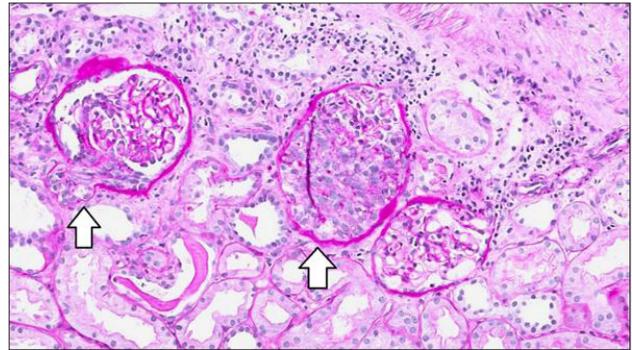


Fig. 1. Kidney biopsy. Up to 45% of visible glomeruli reveal cellular crescents (white arrows). Periodic acid-Schiff stain, 200x

After the initial treatment, the patients' diuresis increased, urea and creatinine levels were relatively diminished (27 and 330 $\mu mol/L$). A second course of treatment was assigned due to the persisting renal dysfunction.

On the 35th day of hospitalization (6 days after the second course of treatment was initiated) a control chest X-ray (Fig. 2) and a subsequent chest CT (Fig. 3) showed a new focal infiltration in the upper lobe of the left lung and a pleural effusion.

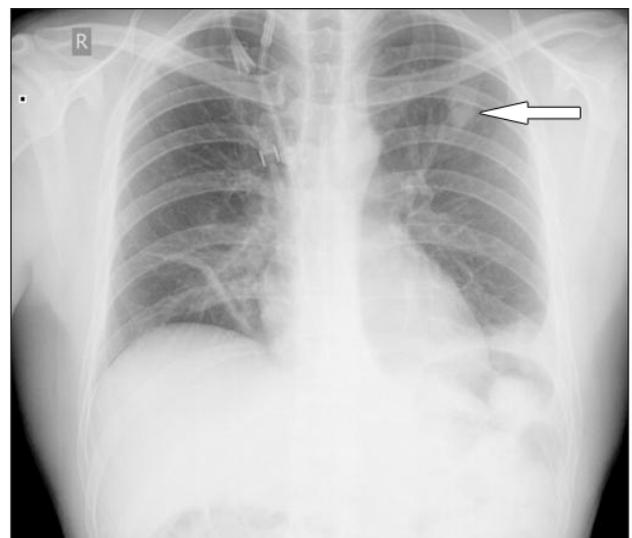


Fig. 2. Chest X-ray image. Local infiltration in the upper lobe of the left lung (white arrow)



Fig. 3. Chest CT image. Infiltrations in the apical lobes with signs of cavitation

Testing for D-dimer (1445 $\mu\text{g/L}$, upper normal limit 250 $\mu\text{g/L}$) and discovering an acute thrombosis of the right cephalic vein during the Doppler ultrasound examination led to the diagnosis of acute pulmonary artery embolism and a pulmonary infarction. Treatment with oral anticoagulants was initiated. A biopsy to evaluate for a possible vascular pathology in the lungs was not performed due to the patients' severe condition.

23 days after the second course of cyclophosphamide and a high-dose glucocorticoids treatment, the patient started to complain of a pain on the site of the left scapula, a fatigue and hemoptysis. The chest X-ray (Fig. 4) and CT (Fig. 5) re-

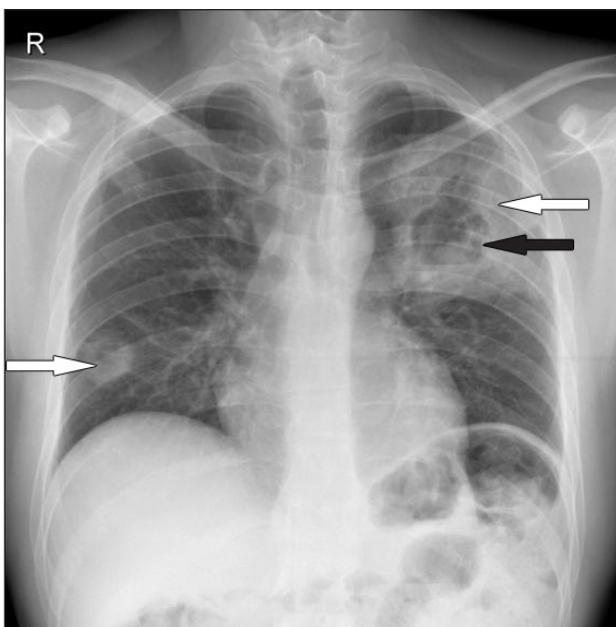


Fig. 4. Chest X-ray image. Polysegmental infiltration with tissue destruction (white arrows) and a mass resembling an abscess (black arrow) in the left lung

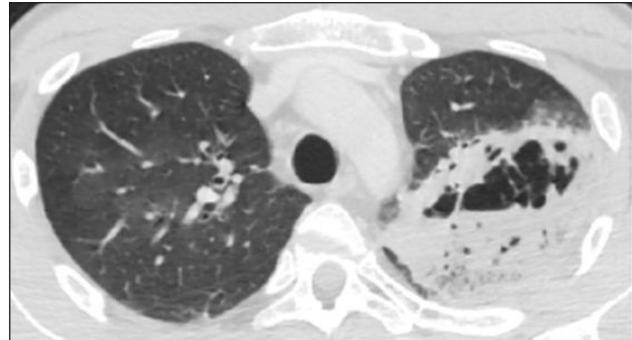


Fig. 5. Chest CT image. A consolidation with multiple cavities in the left lung

vealed a solid structure and a thick wall pulmonary cavity in the right lung, multiple cavities and a consolidation in the left lung.

Those findings of pulmonary tissue destruction were interpreted as a progression of a vascular pathology process.

Prior to the third course of the treatment an infectious complication of immunosuppressive therapy was suspected. The patient was treated with imipenem/cilastatin and vancomycin. A fibrobronchoscopy with bronchoalveolar lavage (BAL) was performed to exclude the possibility of a fungal infection and tuberculosis. The smears and cultures for *Mycobacterium tuberculosis*, *Pneumocystis jirovecii* and fungi were negative. Unfortunately, the galactomannan level was not evaluated. However, the treatment with fluconazol was initiated. ANCA titer diminished to normal. During the week after the initiation of the third course of therapy, the patient developed multiple

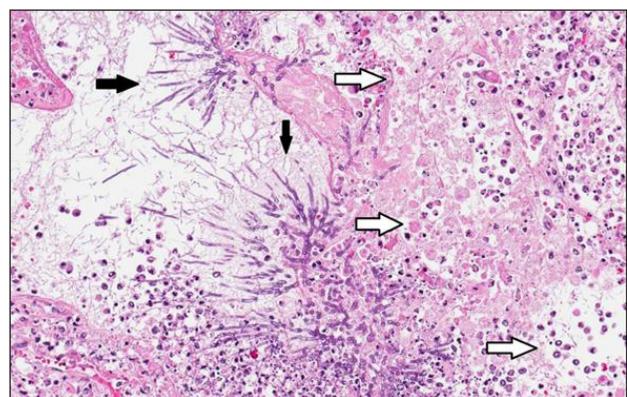


Fig. 6. Lung sample. Areas of necrosis (white arrows) with star-shaped angioinvasive *Aspergillus* fungi colonies (black arrows) (hematoxylin and eosin stain, magnification $\times 200$)

pneumothoraces, his respiratory and renal dysfunction worsened. The patient died 4 days later.

The autopsy report disclosed AAV with renal and pulmonary impairment as the main cause of death. The presence of vasculitis was also noticed in the coronary arteries. The complications included disseminated angioinvasive *Aspergillus* fungal infection (bilateral fungal pneumonia (Fig. 6), abscesses in the lower lobes of both lungs, an abscess localized in the head of the pancreas and parapancreatic tissue).

DISCUSSION

Even in patients with known vasculitis it is challenging to differentiate between a progression of the disease, a complication of a drug therapy, an underlying infection or a combination of these conditions due to their similar presentation (6). In our case respiratory and renal systems were involved. ANCA titers have been shown to correlate highly with disease activity. C-ANCA is associated with GPA with 90–95% sensitivity and 90% specificity in generalized disease. In our case one of the most important findings that led to an AAV diagnosis was a positive test for ANCA titers (c-ANCA pattern).

CT scanning is the most sensitive for the detection of lung involvement in AAV. Nodules and masses are seen in up to 90% of patients: they are usually multiple and bilateral. They also seem to have a tendency towards cavitation. These findings while being non-specific are useful for characterization of the disease manifestations (7, 8). In our case infiltrations were seen in the initial CT scan.

Unfortunately, the pulmonary tissue destruction was interpreted as a progression of this vascular pathology process. Although we were not able to confirm the etiology of the ongoing process in the lungs due to the lack of the lung biopsy, a course of treatment had to be initiated right away because of the patient's renal function decreased rapidly.

Cyclophosphamide and glucocorticoids are consistently recommended as the 'standard of care' for AAV. Clinical deterioration under immunosuppressive treatment should raise a suspicion of an infection, treatment resistance or a relapse of the disease. The autopsy of our patient revealed an invasive pulmonary aspergillosis (IPA). Many authors state that diagnosing IPA is difficult due to the low specificity and sensitivity of the clinical

signs, radiologic changes microscopy and cultures of the BAL fluid (8, 9–13).

In our case, a fibrobronchoscopy with BAL were performed, but the culture and direct microscopy for fungi were negative. The reported sensitivity of a direct microscopy is variable from 0 to 90% (9). Microscopic examination should not be considered as an early diagnostic technique (14). It is also known that culture of the fluid collected during BAL typically has a low sensitivity and specificity, especially during the early stages of the disease (8, 10, 11).

Recent studies of the efficacy of serum galactomannan (GM) to diagnose invasive aspergillosis suggest that assays sensitivity varies from 13 to 88% while the specificity ranges from 21 to 100% (9). In non-neutropenic patients with aspergillosis the sensitivity of serum GM detection is not greater than 50%. This limits the use of the method as a diagnostic technique (12). Detection of fungal markers in the BAL fluid has a higher sensitivity and specificity (10).

Although there is debate about the expedience of antifungal prophylaxis even in high-risk patients, prophylactic strategies may be useful for patients who are at a high risk for invasive aspergillosis, but the selection of this specific group remains challenging. Voriconazole is recommended for the primary treatment of IPA in most patients (6).

In conclusion, our report shows that fatal angioinvasive pulmonary *Aspergillus* infection may occur during induction therapy in vasculitis patients. In case of a discrepancy between the improvement of the kidney symptoms and a deterioration of the pulmonary state during an immunosuppressive therapy, an invasive aspergillosis has to be suspected, and an appropriate testing (including microbiological and serological tests of the blood and BAL fluid) and antifungal therapy should be initiated.

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MIRTINOS KOMPLIKACIJOS SKIRIANT REMISIJĄ INDUKUOJANTĮ GYDYMĄ SERGANTIEMS ANCA-ASOCIJUOTU VASKULITU

Santrauka

ANCA-asocijuotas vaskulitas yra sisteminė uždegiminė liga, kuria sergant pažeidžiamos ne tik plaučių, bet ir kitų organų mažosios bei vidutinio dydžio kraujagyslės. Remisiją indukuojančios terapijos tikslas – kiek įmanoma greičiau sumažinti uždegimą ir ligos simptomus, išvengti negrįžtamo audinių pažeidimo. Skiriamas imunosupresinis gydymas gali sukelti infekcines komplikacijas, iš kurių rečiausia ir sunkiausia – invazinė grybelinė infekcija.

Straipsnyje pristatome 29 metų amžiaus vyro, kuriam diagnozuotas ANCA-asocijuotas vaskulitas, klinikinį atvejį. Kliniškai pokyčiai plaučiuose buvo traktuoti kaip vaskulito progresija, tačiau skiriant remisiją indukuojantį gydymą ligoniui išsivystė sunki invazinė aspergiliozės forma, todėl jis mirė. Straipsnyje aprašoma ligos eiga, pristatomi radiologinių ir histologinių tyrimų vaizdai, aptariamas gydymas ir pateikiama literatūros apžvalga.

Raktažodžiai: ANCA-asocijuotas vaskulitas, imunosupresinis gydymas, invazinė aspergiliozė