

Invasive aspergillosis successfully treated by combined antifungal therapy and immunosuppressive monotherapy two months following heart transplantation



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Abstract

Invasive aspergillosis is becoming increasingly prevalent, especially following transplantation. Invasive aspergillosis is associated with mortality. Successful therapy is related to early diagnosis and proper therapy. We present the case of a 61-year-old man suffering from invasive aspergillosis 2 months following heart transplantation. He was suffering from hypertrophic cardiomyopathy and he underwent orthotopic heart transplantation. He was readmitted to the Department of Cardiology 69 days following transplantation due to symptoms of productive cough for 5 days. It was accompanied by chest pain, shortness of breath, and fever up to 39°C. He was slightly cyanotic and confused on physical examination. The patient's status deteriorated within the following 2 days. On bronchoscopic specimen examinations *Aspergillus* mould filaments were detected and the serum galactomannan index was 12.162. His blood saturation decreased to 85%. C-reactive protein serum level increased to 273 mg/l. The patient was admitted to the intensive care unit and intubated due to severe respiratory insufficiency. Computed tomography revealed massive, mostly homogeneous consolidation. The patient was treated with 200 mg of voriconazole and 50 mg of caspofungin daily. Caspofungin therapy was continued for 23 days and voriconazole was administered parenterally for 62 days. Voriconazole therapy was continued orally for 9 months. During combined antifungal therapy, the galactomannan serum index constantly decreased from 12.1 to 0.33 (end-point of caspofungin therapy) and to 0.23 (end-point of voriconazole parenteral administration). His immunosuppressive therapy was limited to calcineurin inhibitor (tacrolimus) monotherapy. Post-treatment imaging 9 months after diagnosis confirmed the efficacy of therapy as a lack of pulmonary infiltration associated with left apical peribronchial scarring as a result of treatment. The

Streszczenie

Grzybica kropidlakowa płuc, zwykle wywołana przez grzyby z rodzaju *Aspergillus*, stanowi najczęstszą postać inwazyjnej grzybicy układu oddechowego po operacji transplantacji serca. Zakażenie płuc tym patogenem, nierozpoznane we wczesnym stadium lub nieskutecznie leczone, wiąże się z ryzykiem wystąpienia powikłań śmiertelnych. Przedstawiamy przypadek 61-letniego chorego z rozpoznaniem aspergillozy płuc w ciągu 2 miesięcy od zabiegu ortotopowego przeszczepu serca. Pacjenta poddano operacji z powodu niewydolności krążenia wtórnej do kardiomiopatii przerostowej. Chory został przyjęty w trybie pilnym, początkowo, na oddział kardiologii, w 69. dniu po procedurze podstawowej, z objawami duszności i kaszlu trwającego od 5 dni. Towarzyszyły mu ból w klatce, zasinienie powłok skórnych, zaburzenia świadomości i temperatura ciała 39°C. Stan chorego uległ stopniowemu pogorszeniu w czasie kolejnych 2 dni. Wynik wykonanego badania mikrobiologicznego uzyskanego podczas bronchoskopii drzewa oskrzelowego potwierdził obecność strzępek grzyba, a stężenie galaktomannanu oszacowano na poziomie wartości 12,162. Podczas hospitalizacji obserwowano wzrost poziomu białka C-reaktywnego w surowicy do 273 mg/l oraz spadek stopnia saturacji krwi do 85%. Pacjent został przyjęty na oddział intensywnej terapii oraz wymagał wentylacji mechanicznej. W badaniu tomografii komputerowej klatki piersiowej rozpoznano masywne zagęszczenia mięszu płucnego. Rozpoczęto terapię przeciwgrzybiczą skojarzoną z 200 mg/dobę vorikonazolu oraz 50 mg/dobę kaspofunginy. Terapię za pomocą kaspofunginy kontynuowano przez okres 23 dni, a vorikonazolu przez 9 miesięcy, obejmujący 62 dni terapii parenteralnej. W trakcie leczenia indeks galaktomannanu zmniejszył się z wartości 12,1 do 0,33 (na końcu terapii kaspofunginą), a następnie do 0,23 (koniec podań dożylnych vorikonazolu).

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present case proved the efficiency of combined (voriconazole and caspofungin) antibiotic therapy in invasive pulmonary aspergillosis. Computed tomography findings followed by the serum galactomannan index are useful tools for early diagnosis. Additional modification of the immunosuppressive regimen can be performed safely in the early postoperative period in case of severe infection.

Key words: heart transplantation, aspergillosis, fungal infection.

Introduction

Invasive aspergillosis is becoming increasingly prevalent, especially following transplantation. The incidence of invasive fungal infections following solid organ transplantation varies from 1.4% to 42% [1]. Invasive pulmonary aspergillosis (IPA) is a more common etiology of fungal infections in heart transplantation recipients than candidiasis [2]. Although there are advances in therapeutic and diagnostic possibilities, invasive aspergillosis is associated with as high as 60-85% mortality rate [3-6]. Successful therapy is related to early diagnosis that usually relies on culture and computed tomography (CT) findings [7].

We present the case of a 61-year-old man suffering from invasive aspergillosis two months following heart transplantation.

Case report

He was suffering from hypertrophic cardiomyopathy and he underwent orthotopic heart transplantation with the lower Shumway technique. He was awaiting urgent heart transplantation due to repetitive pulmonary edema episodes despite inotropic support. Cold ischemia time was 216 minutes, and cross clamping time was 142 minutes. Induction therapy including basiliximab was applied. The postoperative period was complicated by pericardial effusion treated by surgical drainage on the 12th day. Decubitus ulcers of both heels were noted during intensive care unit stay and they required surgical interventions. He stayed 41 days in the intensive care unit and overall postprocedural hospitalization time was 53 days.

Postoperative echocardiography was satisfactory, with left ventricle ejection fraction of 73% and intraventricular septum diameter below 12 mm. Routine blood tests on discharge revealed normal white blood count ($5 \times 10^9/l$), hemoglobin concentration (7.3 mmol/l) and platelet count ($367 \times 10^3/l$). Protocol endomyocardial biopsies performed on the 8th, 23rd and 38th day were negative for rejection (grade 0 according to International Society for Heart and Lung Transplantation criteria). He was discharged on triple standard immunosuppressive therapy including tacrolimus (serum concentration 11 mg/l), mycophenolate mofetil (serum concentration 2 mg/l) and prednisolone (20 mg daily). An early marker of cytomegalovirus infection (pp65) was negative throughout the hospitalization.

He was readmitted to the Department of Cardiology at 69 days following transplantation due to complaints of pro-

ductive cough for 5 days. It was accompanied by chest pain, shortness of breath, and fever up to 39°C. He was slightly cyanotic and confused on physical examination.

Słowa kluczowe: transplantacja serca, *Aspergillus*, kropidlak, grzybica płuc.

ductive cough for 5 days. It was accompanied by chest pain, shortness of breath, and fever up to 39°C. He was slightly cyanotic and confused on physical examination.

A routine blood test showed no pathological results except leucopenia ($3.4 \times 10^9/l$) and an increased level of the inflammatory marker C-reactive protein (43.8 mg/l). Blood saturation was 92% and chest X-ray revealed hypodense masses on the side of the left lung. Serum galactomannan index as part of a routine procedure following transplantation was measured.

Antibiotic therapy including parenteral infusion of piperacillin 4.0 g and tazobactam 0.5 g three times a day was started. Bronchoscopy was performed and specimens for microbiology examinations were taken.

The patient's status deteriorated within the following two days. On bronchoscopic specimen examinations *Aspergillus* mould filaments were detected and the serum galactomannan index was 12.162. His blood saturation decreased to 85%. The C-reactive protein serum level increased to 273 mg/l.

The patient was admitted to the intensive care unit and intubated due to severe respiratory insufficiency. Computed tomography (CT) revealed massive, mostly homogeneous consolidation of left apical segments and patchy infiltration in the right lung. Additionally, bilateral pleural effusion with associated left-sided basal atelectasis was detected (Fig. 1). Computed tomography findings accompanied by laboratory tests and culture confirmed the diagnosis of invasive aspergillosis. The consolidation pattern did not strictly fulfill a certain type of IPA. Peribronchial consolidation and small airway lesions typical for airway invasive pattern were combined with typical internal low attenuation zones and a discrete halo sign related to the angioinvasive form. No typical signs for infarct shaped consolidation and no air crescent sign were detected.

The patient was treated with 200 mg of voriconazole and 50 mg of caspofungin daily. The decision to use a combination of both drugs was based on the severity of fungal invasion. He was extubated on the 8th day following admission. Caspofungin therapy was continued for 23 days and voriconazole was administered parenterally for 62 days. Voriconazole therapy was continued orally for 9 months. During combined antifungal therapy, the galactomannan serum index constantly decreased from 12.1 to 0.33 (end-point of caspofungin therapy) and to 0.23 (end-point of voriconazole parenteral administration).

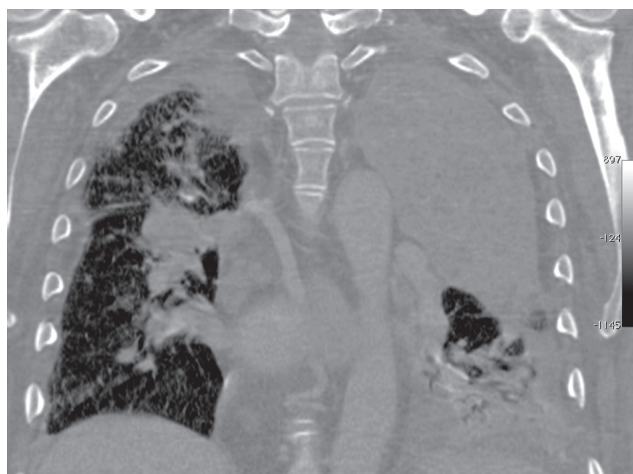


Fig. 1. Computed tomography scan prior to therapy, revealing invasive aspergillosis. Axial and coronal maximum intensity projection (MIP) images – massive mostly homogeneous consolidation of left apical segments and patchy infiltration in right lung. Additionally bilateral pleural effusion with atelectasis in left basal segments



Fig. 2. Computed tomography scan following antifungal therapy. Follow-up 9 months after initial CT imaging. Scans at the corresponding level reveal no retaining infiltration. Remaining peribronchial scarring in left apical segments as a result of treatment

His immunosuppressive therapy was limited to calcineurin inhibitor (tacrolimus) monotherapy. Steroids and antiproliferative mycophenolate mofetil were withdrawn due to severe infection. Calcineurin inhibitor serum concentration was at therapeutic levels (mean 12 ± 2 mg/l).

Follow-up CT imaging on a regular schedule presented continuous regression of pulmonary lesions. Post-treatment imaging 9 months after diagnosis confirmed the efficacy of therapy as a lack of pulmonary infiltration associated with left apical peribronchial scarring as a result of treatment (Fig. 2).

Discussion

There is a high percentage (up to 40%) of *Aspergillus* lung colonization in the general population [8]. In immunocompetent organisms antifungal defensive protection includes mechanical barriers, phagocyte activation and antimicrobial peptide release. The airways are the most frequent ports for invasion, especially in immunocompromised patients and especially following transplantation. The other predisposing risk factors for developing invasive aspergillosis that have been reported include severe and prolonged neutropenia, allogeneic stem cell transplantation, and prolonged use of corticosteroids [9, 10]. The etiology of this fungal infection in heart transplantation recipients is more frequently aspergillosis than candidiasis.

Invasive pulmonary aspergillosis in immunocompromised patients can be classified into two different patterns based on CT imaging pattern. *Aspergillus* may invade blood vessels, causing hemorrhagic infarction that is called angio-invasive aspergillosis. It can cause tracheobronchitis, bronchiolitis or pneumonia, being classified as airway-invasive aspergillosis. Each of the types has a distinct histologic pattern and CT appearance [11]. Computed tomography is one of the essential examinations performed for non-invasive diagnosis of fungal infection. An angio-invasive pattern typically comprises an infarct-shaped consolidation, a halo sign and an internal low attenuation, cavity or crescent sign. Small airway lesions as small, clustered or centrilobular micronodules and branching linear opacities, a peribronchial consolidation and a bronchiectasis support the diagnosis of an airway-invasive form [12-14].

Successful therapy is related to early diagnosis that usually relies not only on computed tomography findings. Apart from imaging tools, microbiology and histopathology diagnostics are necessary. Instead of microbiology culture, a serum *Aspergillus* antigen named galactomannan has been reported as a reliable test for detecting invasive aspergillosis [15, 16]. By using galactomannan (GM), a prompt diagnosis can be established a few days earlier compared to other methods [17]. The galactomannan index can be determined in serum and BAL samples. Although some residual GM might still be present in piperacillin/tazobactam, currently available brand piperacillin/tazobactam preparations seem no longer responsible for false-positive GM results [18]. The patient was treated with piperacillin/tazobactam prior to galactomannan examination in the present study.

The combination of both antifungal drugs – voriconazole and caspofungin – was reported to have better results than caspofungin monotherapy. Azoles target the fungal cell membrane and echinocandins act on the cell wall. Voriconazole monotherapy is claimed to be associated with lower *Aspergillus*-related mortality compared to caspofungin alone [19]. Caspofungin is approved for therapy in patients who experience failure with other antifungal drugs [20, 21].

The gold standard in diagnosis of *Aspergillus* infection is histopathological examination of pulmonary lung tissue

[22, 23]. Such examination allows for the exclusion of malignancy or non-fungal infectious diseases. Histopathological examination is not only invasive but also requires time to obtain a proper diagnosis. In acute pulmonary insufficiencies, as presented in our study, noninvasive diagnostic tools (computed tomography and serum galactomannan index) are the best options.

Surgical resection is one of the possible therapeutic interventions, too [24-27]. It may prevent further aspergillosis spread to other organs. Indications for resection are limited to hemoptysis, pulmonary lesions that are contiguous with major blood vessels or pericardium and chest wall invasion. The safety of surgical resection in immunocompromised patients has been reported [28]. Efficiency of combined antibiotic therapy reported in our study excluded the risk for surgical partial lung resection.

Standard immunosuppression following heart transplantation is a calcineurin inhibitor based triple-drug regimen [29]. Monotherapy is limited to rare situations [30]. Mycophenolate and steroids early withdrawal is rare in clinical practice despite good mid-term survival and low rates of allograft rejection and vasculopathy in the TICTAC trial [31]. Kidney recipients can be successfully treated with long-term maintenance immunosuppression monotherapy, especially in case of mycophenolate intolerance [32]. Good results of tacrolimus monotherapy in late postoperative follow-up has been described in retrospective analysis so far [33]. In our case, immunosuppression was limited due to severe fungal infection in the early period (2 months after surgery). Although it was performed 2 months following transplantation, there were no episodes of rejection within the first postoperative year.

Conclusions

The present case proved the efficiency of combined (voriconazole and caspofungin) antibiotic therapy in invasive pulmonary aspergillosis. Computed tomography findings followed by the serum galactomannan index are useful tools for early diagnosis. Additional modification of the immunosuppressive regimen can be performed safely in early postoperative period in case of severe infection.

Disclosure

Authors report no conflict of interest.

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