

Successful Treatment of Pseudomembranous Necrotizing *Aspergillus* Tracheobronchitis in a Patient with Acute Myeloid Leukemia

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SUMMARY

Introduction Pseudomembranous necrotizing *Aspergillus* tracheobronchitis is a rare form of pulmonary aspergillosis which occurs in immunocompromised patients.

Case Outline A female patient aged 71, suffering from acute myeloid leukemia, developed the symptoms of progressive shortness of breath and inspiratory stridor. The diagnosis in our case was made on the histological findings from tissues obtained by bronchoscopy. A chest CT scan suggested the state of the compromised trachea and left principal bronchus lumen. The long-term regimen with itraconazole in the dose of 400 mg/24 hours proved efficient in our patient.

Conclusion Progressive shortness of breath and inspiratory stridor in immunocompromised patients along with radiological and CT changes should be also considered as pulmonary aspergillosis in differential diagnosis.

Keywords: aspergillosis; acute myeloid leukemia; trachea; large bronchi; immunodeficiency; antifungal medicament

INTRODUCTION

Pseudomembranous necrotizing *Aspergillus* tracheobronchitis (PNTB) is a rare form of invasive pulmonary aspergillosis which occurs in immunocompromised patients, primarily those with neutropenia, hematological disorders, acquired immunodeficiency syndrome (AIDS), and patients who underwent bone marrow or organ transplantation. The diagnostic criteria include *Aspergillus* isolation from the cultures of tracheobronchial tree samples, or the histological confirmation of *Aspergillus* in the affected tissue, along with confirmation of the absence of alternative diagnosis, as well as the absence of radiological, clinical and histological evidence of invasive parenchymal aspergillosis [1].

Aspergillus tracheobronchitis (ATB) can be manifested as obstructive tracheobronchitis, ulcerative tracheobronchitis and PNTB, the latter being the most unfavorable form of ATB. PNTB is known to have a fatal outcome in 90% of patients, regardless of the administered antifungal drug [2-5]. The degree of immune dysfunction is crucial for treatment outcome [4].

CASE REPORT

A 71-year-old female patient, non-smoker, was admitted at the Institute for Pulmonary Diseases of Vojvodina as an emergency case, with dyspnea, orthopnea and inspiratory stridor, immediately after completed second chemo-

therapy course (cytosine arabinoside + daunoblastin) according to the protocol for acute myeloblastic leucemia (AML). There were no other illnesses before. Laboratory findings revealed leukocytosis (WBC $13.9 \times 10^9/L$), erythrocyte count of $3.59 \times 10^{12}/L$, hemoglobin 113 g/L, and platelets $301 \times 10^9/L$. Biochemistry findings involving glucosa, urea, creatinine, sedimentation rate, C-reactive protein (CRP), fibrinogen, and coagulation status were within the reference values range, except for lactate dehydrogenase (LDH) that was 240 U/L. On admission the patient showed global respiratory failure with tachypnea within 24 min. Oxygen saturation was 94%, oxygen partial pressure of 10:00 kPa and carbon dioxide 6:54 kPa.

The standard chest X-ray finding revealed extended shadow of the upper mediastinum and cardiac vessel shadows, with reduced transparency at lung bases. The CT scan of the chest revealed a stricture in the lumen of the trachea and the left main bronchus, as well as a moderate mediastinal lymphadenomegaly. Extended cardiac structures and stain-like lesions of the lung parenchyma were detected primarily in the lower lobes of both lungs (Figure 1). Bronchoscopic examination showed normal findings of the larynx, but with strictures of the trachea and with hyperemic mucosa which abundantly bled during contact with the instrument. The tracheal lumen was covered with necrotic, soft yellowish masses. The masses were partially covering tracheal mucosa in the form of a pseudo membrane, which reduced the lumen of the trachea. This content was also present at

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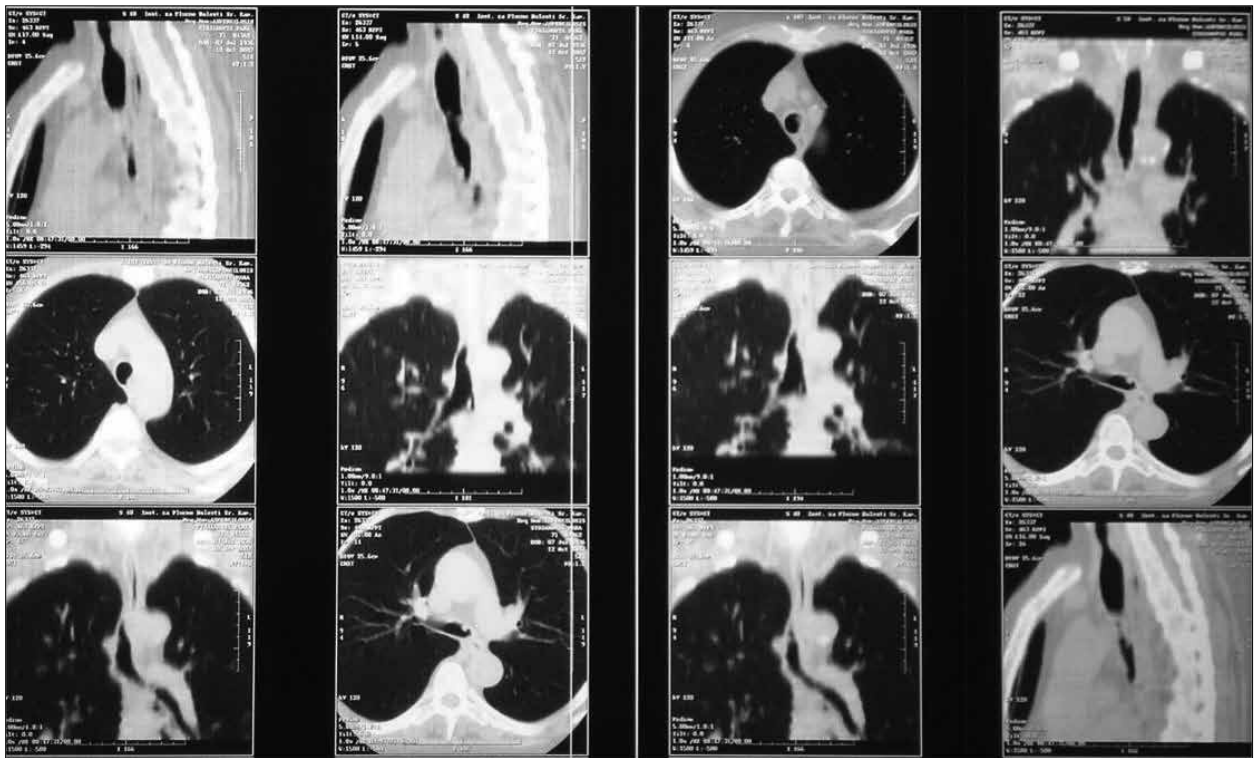


Figure 1. Thoracic CT scans



Figure 2. First bronchoscopy shows whitish fungal plaques obstructing the lower trachea

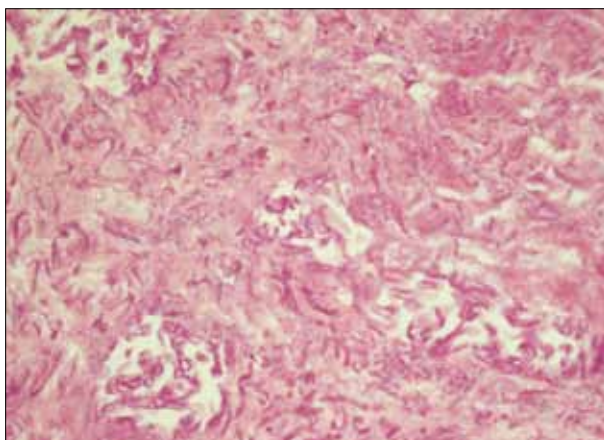


Figure 3. Numerous *Aspergillus hyphae* in necrotic tissue (HE, 200x)

the bifurcation and at the orifice of the left main bronchus (Figure 2). The bronchial biopsy sample revealed a piece of bronchial mucosa, which surface was partially ulcerated and partially covered by a yellowish pseudomembrane, of which the necrotic lamina propria was composed, and was also permeated with fibrinous threads and thick lymphocyte infiltrates, plasma cells and neutrophilic granulocytes. Within pseudomembranes and blood vessel lumens of the lamina propria, there were numerous branched hyphae of the *Aspergillus* strain fungus, confirmed by PAS (Periodic acid-Schiff) and GMS (Gomori methenamine silver) staining methods. The definite histopathological diagnosis was pseudomembranous necrotizing bronchial aspergillosis (PNBA) (Figure 3).

Treatment was initiated immediately after admission, including a controlled oxygenation using a 24% volume mask, crystalloid infusions, bronchodilators, gastroprotective drugs, short-term insulin and thyroid hormones substitution. Oral itraconazole 2x200 mg/24 hours was introduced in the treatment following seven weeks.

In the following seven days, the patient responded to the applied treatment with improved dyspnea and inspiratory stridor. The maintenance dose (2x100 mg/24 hours) proved sufficient to achieve a control of the respiratory symptoms induced by PNTB during the 4-month period after the diagnosis. Five days after bronchoscopy, CT for three-dimensional visualization of the trachea and large bronchi (virtual bronchoscopy) was performed, detecting a few exophytic, polypoid and sessile lesions with regular, arch-shaped contours with the following localizations: sublaryngeal on the right, next to the left lateral wall of the trachea at the level of the aortic arch, next to the carina of the trachea, and in the left main bronchus with deformed



Figure 4. Bronchoscopy after therapy without fungal plaques

and thickening bronchial all along. The precipitation test finding for *Aspergillus* was negative. The bronchoscopy performed 21 days after the initial one, showed general improvement. The lumen of the trachea was free, without pseudomembranes (Figure 4). The left main bronchus was deformed in shape of circular stenosis, with vulnerable mucosa which was bleeding on contact. The right main bronchus was passable. During hospitalization, additional virtual bronchoscopy was also performed, confirming satisfactory regression of the registered exophytic endoluminal lesions.

DISCUSSION

Invasive pulmonary aspergillosis makes 90% of all clinical forms of pulmonary aspergillosis, and 7-20% of these infections are manifested by a concurrent involvement of the tracheobronchial tree [1]. As an isolated form of invasive pulmonary aspergillosis, PNBA is found in 7-10% of the affected patients [6].

ATB may be manifested in the form of aspergillus bronchitis, obstructive tracheobronchitis, ulcerative tracheobronchitis, and PNBA [2-6]. New classification divides ATB in immunodeficient patients into three forms [7, 8, 9]: 1) mucous deposits and plaques with no inflammatory response signs in the bronchial mucosa (this form is usually found in the patients with heart transplantation and AIDS); 2) pseudomembranous aspergillosis of the tracheobronchial tree accompanied by an extensive inflammation with pseudomembranous deposits covering the mucosa and containing *Aspergillus*; 3) ulcerous aspergillosis of the tracheobronchial tree manifested as a local infection in the region of the pulmonary transplant suture – this form has a good prognosis and a good response to instillation of antifungal drugs during bronchoscopy and to surgical debridement [1].

We report a very rare case of pseudomembranous necrotizing aspergillosis of the large airways in the form of the local invasive aspergillosis of the trachea and bronchi, emphasizing a characteristic appearance of intraluminal,

superficial and circumferential pseudomembranes containing fibrin and *Aspergillus hyphae* that resulted in the obstruction of the airways with persisting fever despite the applied antibiotics. The diagnosis can be based on the identification of the agent in sputum, bronchial lavage fluid, broncho-alveolar lavage fluid (BAL), transthoracic percutaneous needle aspiration sample or biopsy sample [10]. Blood cultures are less useful for diagnosis even in disseminated infections. The diagnostic method of choice is bronchoscopy with bronchobiopsy, but attention should be raised due to the risk of bleeding during the intervention and sampling. Galaktomannan (GM), antigen, residing in *Aspergillus hyphae*, may be diagnostically relevant in cases of invasive forms of pulmonary aspergillosis.

The treatment approach depends on the clinical criteria including the severity of immunosuppression, the underlying disease, and the infection site. Results indicated that variconazole had an advantage over amphotericin B, so variconazole was recommended as the first-line drug [1]. High cost of treatment makes variconazole unavailable for low income countries. The administration of amphotericin can be associated with high nephrotoxicity and undesirable side effects after administration, including fever, myalgia, nausea, vomiting, headache and bronchospasm.

The application of combined therapy regimens including amphotericin B in the lipid form, posaconazole, itraconazole, caspofungin or micafungin, has not been entirely standardized so far, thus additional clinical trials are required. In patients refractory to variconazole, the therapy of choice is amphotericin B, although resistance to one antifungal drug often involves resistance to others as well, as is the case with variconazole and itraconazole [1].

However, in this paper we presented the regression of symptoms after using classical antifungal drug itraconazole. Literature data have indicated that itraconazole induces a partial or complete response in 39-52% of the patients. The most common side effects of itraconazole include transient nausea and elevated liver aminotransferase levels. Gastrointestinal intolerance is more common with oral administration of the drug. As itraconazole may occasionally induce inotropic effect, it should cautiously be applied in patients with left ventricle dysfunction [1, 8, 9]. Prophylaxis with posaconazole is recommended during bone marrow transplantation in patients with leukemia or myelodysplastic syndrome [7, 8].

Any progressive dyspnea and inspiratory stridor in immunodeficient patients with radiographic and CT verification of the chest lesions suggest to be considered as PNTB in the differential diagnosis and request appropriated treatment.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant number 175056).

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Успешно лечење псеудомембранозног некротичног трахеобронхитиса изазваног аспергилусом код болеснице с акутном мијелоидном леукемијом

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КРАТАК САДРЖАЈ

Увод Псеудомембранозни облик инфекције *Aspergillus tracheobronchitis* је ретка инфекција плућа која се јавља код особа нарушеног имунског система.

Приказ болесника Болесница стара 71 годину која је лечена од акутне мијелоидне леукемије примљена је са симптомима прогресивног отежаног дисања и инспираторним стридором. Дијагноза је постављена на основу хистолошког налаза ткива добијеног бронхоскопијом. Снимак компјутеризоване томографије (СТ) је указивао на захваћеност трахеје и лумена левог главног бронха. Дуготрајно лечење

антимикотиком итраконазолом у дози од 400 mg дневно довело је до излечења ове болеснице, што је потврђено и на контролном СТ снимку.

Закључак Прогресивно отежано дисање и инспираторни стридор код болесника нарушеног здравља заједно с радиолошким испитивањима и СТ грудног коша указује на то да треба обратити пажњу на могућност постојања плућне аспергилозе у диференцијалној дијагнози.

Кључне речи: аспергилоза; акутна мијелоидна леукемија; трахеја; имунодефицијенција; антимикотици

Примљен • Received: 16/09/2013

Прихваћен • Accepted: 24/03/2014