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Pulmonary mycobacteriosis caused by *mycobacterium kansasii* as a precede to the chronic pulmonary aspergillosis: case report

Mikobakterioza pluća uzrokovana *mycobacterium kansasii* kao prethodnica u kroničnu plućnu aspergilozu: prikaz slučaja

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Abstract. ***Aim:*** To present a patient suffering from chronic pulmonary aspergillosis and in whom a prolonged use of corticosteroids due to chronic obstructive pulmonary disease represented a serious risk factor in the development and progression of the infection. ***Case report:*** We present a case of a 52-year-old cachectic, HIV seronegative potator and smoker who, having recovered from pulmonary mycobacteriosis caused by Mycobacterium kansasii, developed a chronic cavitary pulmonary aspergillosis (CCPA) which was confirmed by radiological, microbiological (positive culture findings on Aspergillus fumigatus in sputum samples, bronchial aspirate and bronchoalveolar lavage) and blood findings (IgG antibodies and a positive galactomannan antigen for Aspergillus).Granulomatous reaction without a hyphal invasion was confirmed by transbronchial lung biopsy. Despite being treated with peroral and intravenous antifungal medicines, the patient died, most probably due to the development of a more invasive form of pulmonary aspergillosis. ***Conclusion:*** Due to the lack of unambiguous diagnostic and therapeutic criteria, chronic pulmonary aspergillosis poses a considerable challenge to the clinician, because it is the case of a continuous disease which shows different forms of clinical and radiological presentation in its evolution. Its relatively high morbidity and mortality rate , despite targeted antifungal therapy, proves the need for further researches, particularly those which refers to the identification of certain presentations of the disease and efficacy of therapeutic methods.

Key words: antifungal treatment; *Aspergillus fumigatus*; chronic cavitary pulmonary aspergillosis; chronic pulmonary aspergillosis; *Mycobacterium kansasii*

Sažetak. ***Cilj:*** Prikazati pacijenta koji boluje od kronične plućne aspergiloze i kod kojega je dugotrajna primjena kortikosteroida zbog kronične opstruktivne plućne bolesti predstavljala važan faktor rizika u nastanku i razvoju infekcije. ***Prikaz slučaja:*** Prikazujemo slučaj 52-godišnjeg pacijenta, kahektičnog, HIV seronegativnog potatora i pušača, koji je nakon preboljele plućne mikobakterioze uzrokovane *Mycobacterium kansasii* zadobio kroničnu kavitarnu aspergilozu pluća koja je dokazana na temelju radioloških, mikrobioloških (pozitivne kulture *Aspergillus fumigatusa* u uzorcima sputuma, aspiratu bronha i bronhoalveolarnom lavatu) i krvnih nalaza (IgG protutijela i pozitivan galaktomananski antigen na *Aspergillus*). Transbronhalnom biopsijom pluća dokazana je granulomska reakcija bez hifalne invazije. Unatoč tretmanu peroralnim i intravenskim antifungicima slučaj je završio letalnim ishodom, najvjerojatnije zbog razvoja invazivnije forme plućne aspergiloze. ***Zaključak:*** Zbog nedostatka nedvosmislenih dijagnostičkih i terapijskih kriterija, kronična plućna aspergiloza predstavlja nemali izazov za neposrednog kliničara, tim više što je riječ o kontinuiranoj bolesti koja u svojoj evoluciji iskazuje različite oblike kliničke i radiološke prezentacije. Njen relativno visok morbiditet i mortalitet, unatoč ciljanoj antifungalnoj terapiji, ukazuje na potrebu daljnjih proučavanja, prioritetno onih koji se odnose na identifikaciju pojedinih prezentacija bolesti i efikasnost terapijskih postupaka.

Ključne riječi: antifungalni tretman; *Aspergillus fumigatus*; kronična pulmonalna kavitarna aspergiloza; kronična plućna aspergiloza; *Mycobacterium kansasii*

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INTRODUCTION

The incidence of pulmonary infections caused by nontuberculous mycobacteria (NTM) is steadily increasing and is in some countries higher than the one caused by Mycobacterium tuberculosis. According to medical literature data, the annual incidence of NTM infections in Croatia is from 0.22 to 0.4 cases in 100,000 inhabitants[1,2] and is considerably lower than in countries in the Northern and Western Europe, North America, Australia and Japan. Strains most often associated with pulmonary diseases in Croatia are M. xenopi, M. avium, M. intracellulare, M. abscessus and M. kansasii, which is isolated in only 1% of NTM isolates[2,3]. Although pulmonary infections it causes, have a relatively good prognosis, partly due to high effectiveness of the regimen consisting of classical antituberculotics, a favourable clinical outcome can be compromised by a subsequent infection with Aspergillus spp.[4,5]. The aim of our study is to present diagnostic and therapeutic methods in a patient suffering from chronic pulmonary aspergillosis developed after recovering from pulmonary mycobacteriosis caused by Mycobacterium kansasii.

Infections with Aspergillus fumigatus represent an important cause of morbidity and mortality in patients who suffered structural damage of lung tissue, especially if they receive corticosteroid therapy.

CASE REPORT

This is a case of a 52-year-old cachectic, HIV seronegative potator and smoker in whom inhomogeneous opacities with cavities were radiologically registered in the upper third of both lungs in May 2014. M. kansasii was isolated in four consecutive samples of sputum cultures, while M. intracellulare was isolated in one sample. The regression of symptoms was achieved in the course of a 14-month antibiotic therapy with isoniazid (300 mg), rifampicin (450 mg) and ethambutol (1200 mg) and even 12 sputum samples were culturally negative. A control chest CT scan in August 2015 showed scarring changes in the upper lobes of both lungs. In the left upper lobe it also showed a cavern with the largest diameter of 65 mm with a thin wall of 2 mm, enlarged lymph nodes along the aortic arch (19x11 mm) and the origin of the left subclavian artery (18x16 mm) as well as the cranially retracted left hilum with the retreat of mediastinal structures into the left hemithorax. Due to the high degree of the air flow obstruction (FEV1 1, 25 L or 34% out of expected 3.64 L), he was treated with inhalation bronchodilators and corticosteroids in a daily dose of 920 µg of fluticasone propionate. Early in March 2017, he was hospitalized again due to progressive breathlessness, productive cough accompanied by hemoptysis, chest pain, exhaustion and weight loss. CT thorax scan showed a practically unchanged finding of the cavern of 63 mm in the left upper lobe with no inside content and its wall was 5 mm thicker than before (Figure 1). In addition, pleural fibrosis on the lung apex was detected. Laboratory findings pointed to signs of systemic inflammation: accelerated erythrocyte sedimentation, elevated C-reactive protein level, leucocytosis of peripheral blood without neutropenia and eosinophilia. Hemogram test showed anemia and proteinogram hypoalbuminemia and polyclonal hypergammaglobulinemia.

Aspergillus fumigatus and Candida glabrata were isolated in sputum samples on two separate occasions and blood tests proved a positive indirect haemagglutination assay test on Aspergillus spp., an elevated concentration of IgG on A. fumigatus and a positive galactomannan antigen, so the patient was treated with peroral itraconazole (200 mg daily) during three weeks. Despite bad general condition and respiratory insufficiency, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was done in April, by which other possible illnesses (carcinoma, tuberculosis) were excluded. In bronchial aspirate and bronchoalveolar lavage (BAL) A. fumigatus and C. glabrata were isolated. In the sample of lung tissue obtained by transbronchial biopsy, granulomatous inflammation without the presence of hyphae was diagnosed, while blastoconidia were detected by microscopic analysis of sputum and BAL. Culture findings of four sputum samples showed negative results on M. tuberculosis. Also,

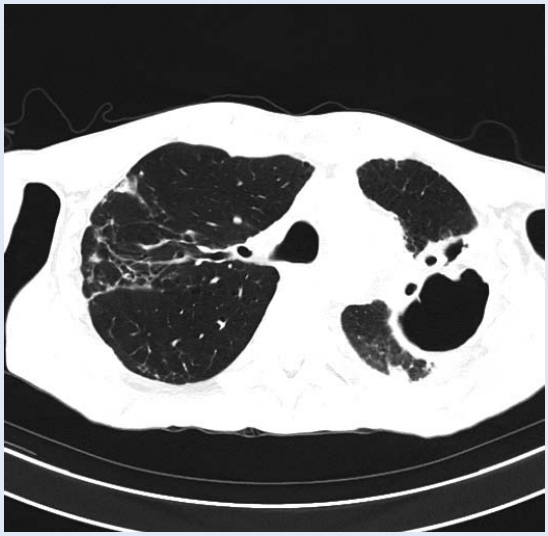

Figure 1. CT thorax scan (March 2017)
On the right in the upper lobe cylindrical bronchiectasis in the perihilar region as well as cystic bronchiectasis predominantly peripherally. On the left in the upper lobe cavity with the diameter of 63 mm, with thick walls, width up to 7 mm, surrounded by cystic bronchiectasis, with which it communicates. Fibrous peribronchial changes.

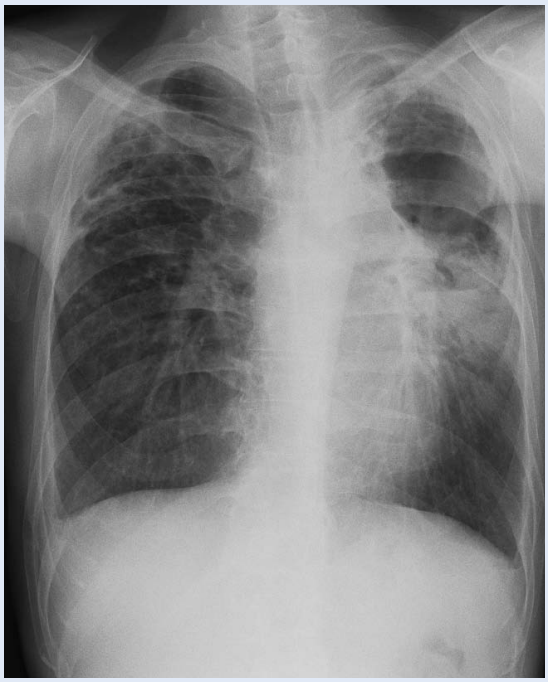

Figure 2. Chest radiograph (July 2017)
Shows an opacity in the left upper lobe with the largest diameter of 80 mm. In a caudal position to it, there is an air-fluid level approx. 40 mm wide that developed inside the destructive zone of parenchyma. Both zones are connected by a spiral ribbon-like opacity, which corresponds to a deformed bronchus.

the bronchial aspirate sample proved negative after direct microscopy. Due to the lack of clinical and radiological response (the increase in the cavity diameter to 80 mm), elevated levels of inflammatory markers as well as the repeated finding of A. fumigatus in sputum and positive galactomannan antigen, an intravenous treatment was started with liposomal amphotericin B. It was prescribed according to antibiogram and administered in a dose of 5 mg/kg of body weight in an overall dose of 54 ml in 250 ml of 5% glucose with the infusion rate of 2,5 mg/kg of body weight per hour. The treatment continued without any notable side effects. Along with antifungal treatment, there was also a dietary support and respiratory rehabilitation, while a dose of inhalation corticosteroids was reduced.

At the beginning of July, the lung radiograph showed a new cavity in a caudal position to the cavity, with air-fluid level which was connected to the apical cavity with a spiral ribbon-like opacity, which was seen as the radiological evolution of the disease (Figure 2). In spite of the continuation of antifungal treatment, the patient deceased 39 months after the first culture of M. kansasii had been isolated from the sputum and 5 months after the first evidence of fungal infection. Post-mortem was not performed.

DISCUSSION

Cavities considered to be predispositional lesions for the infection with Aspergillus spp. were registered by classical radiography in 53% of cases of lung infection with M. kansasii[6], and even in 83% of CT scan findings[7]. According to literature reports, the incidence of mycetoma in cavities after the infection with M. kansasii is 8% and it clinically does not differ from those developed in post tuberculous cavities[4]. It has been established that patients with bronchiectasis and pulmonary mycobacteriosis have higher incidence of additionally suffering from Aspergillus spp. caused lung disease than patients with bronchiectasis, but without mycobacteriosis[8]. Cavitational disease, bronchiectasis and prolonged use of inhalational corticosteroids, alongside chronic alcoholism were important factors of long-lasting immunosuppression and increased risk of developing pulmonary aspergillosis in this patient.

M. kansasii was isolated in sputum cultures in four consecutive samples, while M. intracellulare, a strain belonging to M. avium complex was isolated in one sample. It is generally considered to be more pathogenic than M. avium[9] since certain strains show hypervirulence which may lead to a progressive pulmonary disease and a bad prognosis[10]. In such cases, the clinician is faced with the problem of determining clinical significance of two pathogenic strains of NTM isolated simultaneously, which, as there are still no general rules, he has to resolve by taking an individual approach[11].

Clinicians should be aware of the range of presentational spectrum and the evolutional character of clinical manifestations of this disease which develop independently of antifungal treatment or changes in the condition of the immunological system of the host.

The case is intriguing to the clinician due to the problem of interpreting the significance of positive cultures of A. fumigatus and C. glabrata in the respiratory system samples (sputum, bronchial aspirate, BAL), blood (positive IgG antibodies and galactomannan antigen for Aspergillus), as well as the identification of phenotypic presentation of pulmonary disease caused by A. fumigatus. Positive Aspergillus IgG has a positive predictive value of 100% in distinguishing infected and colonised individuals[12] and represents a gold standard for confirmation of the infection and diagnosis of CPA (chronic pulmonary aspergillosis)[13]. Although recent studies have shown that 23% of patients with CPA have a positive galactomannan test in serum[14], its positive value could indicate an existence of vascular invasion which is not usually characteristic of CPA[15] and a more invasive form of aspergillosis[16]. The absence of both severe immunosuppression, neutropenia and hyphal invasion in the histological lung samples eliminated invasive pulmonary aspergillosis (IPA) diagnosis[17]. Diagnosis of CCPA was made, which is one of the subtypes of CPA[18] affecting patients without obvious immunological deficit, but with predisposing pulmonary diseases such as COPD or previous tuberculous or nontuberculous mycobacterial disease[19] and whose short-term mortality rate in patients treated in hospital is 10 – 30%, and 50% in the period of five years[20].

Diagnosis was corroborated by a piece of information taken from literature according to which half the patients with this disease do not have in CT registered residual cavities a fungal ball, an archetypical but a late sign of infection with A. fumigatus[21]. Thickening of the cavity wall from 2 mm to 7 mm is the consequence of chronicity and thickness itself does not correlate with the activity of the disease[15] and is not a useful marker of the disease activity[22]. The role of C. glabrata is not positively defined in pathological occurrences, likely because it is reputed to be non-pathogenic Candida species present within a normal respiratory flora that rarely causes a disease.

An attempt to treat the patient interdisciplinarily did not succeed. Thoracic surgeon dismissed the possibility of surgical treatment because of high intra and postoperative risk. After a consilliary ckeck-up at the Clinic for Infectious Diseases, the patient was advised to continue with antifungal treatment in the parent institution.

As CPA consists of more clinical entities caused by Aspergillus spp. which can overlap clinically and radiologically and since they can be observed as a continuous spectrum of variable forms of a disease[23] in the process of which one subtype of a disease can in time evolve into another[24] depending on the interactivity of pathogens and the host as well as his immunosuppression, one should not exclude the conclusion that the patient developed a more invasive form of disease that accelerated his death. What we first and foremost have in mind here is chronic necrotizing pulmonary aspergillosis (CNPA), which has recently been known as a subacute invasive aspergillosis (SAIA) or semi-invasive aspergillosis, and which presents itself by gradual increase of the existing cavity or the appearance of new adjacent cavities[23]. Patients with this entity, which was once considered to be an intermediate stage between the chronic infection and invasive aspergillosis[25], differ little from those with CCPA[23] by clinical manifestations and immunological dysfunction.

CONCLUSION

Infections with Aspergillus fumigatus represent an important cause of morbidity and mortality in patients in whom the previous infection with M. kansasii resulted in structural damage of lung tissue, especially if they suffer from bronchiectasis and COPD and receive corticosteroid therapy. Therefore it is important to make a reliable diagnosis founded on the combination of invasive and non-invasive diagnostic methods and administer targeted and most often long-term antifungal treatment. While doing so, clinicians should be aware of the range of presentational spectrum and the evolutional character of clinical manifestations of this disease which develop in the presence or absence of antifungal treatment or changes in the condition of the immunological system of the host.

Conflicts of interest statement: author reports no conflicts of interest.

REFERENCES

1. Janković M, Sabol I, Žmak Lj, Katalinić-Janković V, Jakopović M, Obrovac M et al. Microbiological criteria in non–tuberculous mycobacteria pulmonary disease: a tool for diagnosis and epidemiology. Int J Tuberc Lung Dis 2016;20:934-40.
2. Janković M, Samaržija M, Sabol I, Jakopović M, Katalinić-Janković V, Žmak Lj et al. Geographical distribution and clinical relevance of non–tuberculous mycobacteria in Croatia. Int J Tuberc Lung Dis 2013;17:836-41.
3. Žmak Lj, Janković M, Obrovac M, Katalinić-Janković V. Non-tuberculous mycobacteria. Croatian Journal of Infection 2013; 33:95-101.
4. Maliwan N, Zvetina JR. Pulmonary mycetoma following Mycobacterium kansasii infection. Report of seven cases. Arch Intern Med 1985;145:2180–83.
5. Hafeez I, Muers MF, Murphy SA, Evans EG, Barton RC, McWhinney P. Non-tuberculous mycobacterial lung infection complicated by chronic necrotising pulmonary aspergillosis. Thorax 2000;55:717-9.
6. Matveychuk A, Fuks L, Priess R, Hahim I, Shitrit D. Clinical and radiological features of Mycobacterium kansasii and other NTM infections. Respir Med 2012;106:1472–7.
7. Mogami R, Goldenberg T, Gomes Cytrangulo de Marca P, Carvalho de Queiroz Mello F, José Lopes A. Pulmonary infection caused by Mycobacterium kansasii: findings on computed tomography of the chest. Radiol Bras 2016;49:209–13.
8. Kunst H, Vickremasinghe M, Wells A, Wilson R. Nontuberculous mycobacterial disease and Aspergillus–related lung disease in bronchiectasis. Eur Respir J 2006;28: 352-7.
9. Koh WJ, Jeong BH, Jeon K, Lee NY, Lee KS, Woo SY et al. Clinical significance of the differentiation between Mycobacterium avium and Mycobacterium intracellulare in My. avium complex lung disease. Chest 2012;142: 1482-8.
10. Weiss CH, Glassroth JJ. Pulmonary disease caused by nontuberculous mycobacteria. Expert Rev Respir Med 2012;6:597-613.
11. Maliwan N, Zvetina JR. Clinical features and follow up of 302 patients with Mycobacterium kansasii pulmonary infection: a 50 year experience. Postgrad Med J 2005;81:530-3.
12. Uffredi ML, Mangiapan G, Cadranel J, Kac D. Significance of Aspergilus fumigatus isolation from respiratory specimens of nongranulocytopenic patients. Eur J Clin Microbiol Infect Dis 2003;22:457-62.
13. Dumollard C, Bailly S, Perriot S, Brenier-Pinchart MP, Saint-Raymond C, Camara B. Prospective evaluation of a new Aspergillus IgG enzyme immunoassay kit for diagnosis of chronic and allergic pulmonary aspergillosis. J Clin Microbiol 2016;54:1236-42.
14. Mennink-Kersten MA, Ruegebrink D, Klont RR, Warris A, Blijlevens NM, Donnelly JP et al. Improved detection of circulating Aspergillus antigen by use of a modified pretreatment procedure. J Clin Microbiol 2008;46:1391-7.
15. Godet C, Philippe B, Laurent F, Cadranel J. Chronic pulmonary aspergillosis: An update on diagnosis and treatment. Respiration 2014; 88:162-74.
16. Azoulay E, Afessa B. Diagnostic criteria for invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186:8–10.
17. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. Eur Respir J 2015;47:45–68.
18. Shin B, Koh WJ, Jeong BH, Yoo H, Park HY, Suh GY et al. Serum galactomannan antigen test for the diagnosis of chronic pulmonary aspergillosis. J Infect 2014;68:494-9.
19. Tanase AD, Colita A, Marculescu A, Berteanu C, Streinu Cercel A, Stoica M et al. Using the galactomannan antigen assay in the diagnosis of invasive aspergillosis after hematopoietic stem cell transplantation. Rom J Morphol Embryol 2012;53:379-82.
20. Cosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax 2015;70:270-7.
21. Denning DW, Pleuvry A C, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ 2011;89:864-72.
22. Greene R. The radiological spectrum of pulmonary aspergillosis. Med Mycol 2005;43:147-54.
23. Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. Clin Infect Dis 2003;37:5265-80.24 Hayes EG, Novak Frazer L. Chronic Pulmonary Aspergillosis–Where Are We? And Where Are We Going? J Fungi 2016;2:18.
25. Gefter WB, Weingrad TR, Epstein DM, Ochs RM, Miller WT. 'Semi-invasive' pulmonary aspergillosis: a new look at the spectrum of Aspergillus infections of the lung. Radiology 1981;140:313-21.