**CASE REPORT**

Chronic necrotizing pulmonary aspergillosis

Hronična nekrotizirajuća plućna aspergiloza

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**Abstract**

**Introduction.** Chronic necrotizing pulmonary aspergillosis (CNPA) is a cavitary, infectious process of lung parenchyma with slow progressive course. Vascular invasion and dissemination to other organs are unusual. Case report. We presented a 25-year old man with bilineal acute leukemia who developed pulmonary and systemic symptoms. Chest CT showed nodular consolidations and cavitary lesions in both lungs. Bronchial biopsy revealed necrotic hyphae but it was negative for *Aspergillus* by culture. Serum was positive for antibodies to *Aspergillus*, but it was negative for antigens. A thoracoscopic lung biopsy of the upper left lobe revealed necrosis of lung tissue, with acute and chronic inflammation of the cavity wall and the presence of hyphae consistent with *Aspergillus* species. **Conclusion.** Although confirmation of the diagnosis is difficult, a combination of characteristic clinical, radiological and histological findings and either serological results positive for *Aspergillus* or the isolation of *Aspergillus* from respiratory samples are highly indicative of CNPA.

**Key words:** pulmonary aspergillosis; diagnosis; tomography, x-ray computed; bronchoscopy; biopsy; histological techniques.

**Apstrakt**

**Uvod.** Hronična nekrotizirajuća plućna aspergiloza (HNPA) je infektivni proces prolongiranog toka praćen stvaranjem kavata u plućnom parenchimu. Vaskularna invazija i diseminacija u druge organe su izuzetno retke. **Prikaz bolesnika.** Prikazali smo bolesnika, starosti 25 godina, obolelog od akutne bilinijske leukemije kod koga su se razvili produktivni kašalj i povišena telesna temperatura. Na CT snimku grudnog koša obostrano nađene su mnogobrojne kavitacije i nodularne infiltracije. Bronhobiopsijom iz gornjeg levoj režnja dokazana je infekcija gljivicama *Aspergillus* koja nije potvrđena mikrobiološki, a serološkim pregledom na gljivice dokazana su antitela na *Aspergillus*, ali ne i na antigen. Biopsijom gornjeg levoj režnja otkriven je nekrotičan detritus sa hifama gljivica, a u zidu i u lumenu manjih bronha i bronhiola inflamatomi infiltrat limfocita, neutrofilnih granulocita, džinovskih ĉeļa i hife gljivica koje morfološki odgovaraju *Aspergillus*-u. **Zaključak.** Iako je teško potvrditi dijagnostiku HNPA, karakteristični klinički radiološki i histološki nalazi, uz pozitivne serološke testove ili mikrobiološku potvrdu uzročnika, visoko su indikativni za HNPA.

**Ključne reči:** aspergiloza, pulmonalna; dijagnoza; tomografija, kompjuterizovana, rendgenska; bronhoskopija; biopsija; histološke tehnike.

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**Introduction**

*Aspergillus* is ubiquitous dimorphic fungus that is present worldwide, found in organic debris, dust, compost, foods, spices and rotten plants. More than 200 species of *Aspergillus* have been identified, however, only 19 are known to be pathogenic for humans. The most common species is *Aspergillus fumigatus*, whereas *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus terreus* are frequently responsible for human infection 1. *Aspergillus* spp may cause a variety of pulmonary diseases, depending on immune status and the presence of underlying lung disease. These manifestations range from invasive pulmonary aspergillosis in severely immunocompromised patients, to chronic necrotizing pulmonary aspergillosis (CNPA) in patients with chronic lung disease and/or mildly compromised immune systems. Aspergilloma is mainly seen in patients with cavitary lung disease, while allergic bronchopulmonary aspergillosis (ABPA) is described in patients with hypersensitivity to *Aspergillus* antigens 2.

In fact, CNPA is a rare pathological entity and the available literature is based on case reports and small case series 3-5. CNPA runs a slowly progressive course over weeks to months, and vascular invasion or dissemination to
other organs is unusual. Patients usually present with fever, malaise, fatigue, weight loss, hemoptysis and chronic productive cough. Occasionally, patients may be asymptomatic. A chest radiograph and chest CT scan usually show consolidation, pleural thickening and cavitary lesions in the upper lung lobes. Pleural thickening is considered an early sign of a locally invasive process. Aspergilloma may be seen in nearly 50% of patients. These radiological findings tend to be progressive over weeks to months. Confirmation of the diagnosis requires a histological demonstration of tissue invasion by the fungus and either serological results positive for *Aspergillus* or the growth of *Aspergillus* on culture.

**Case report**

We presented a patient, aged 25, treated for acute bila
eal leukemia at the Department of Hematology, Clinical Centre of Vojvodina from April 2009. In July of the same year the patient was moved to the Institute for Pulmonary Diseases of Vojvodina due to suspected pulmonary aspergillosis, and right sided spontaneous pneumothorax due to which a thoracic drain was placed and bronchoscopic examination was performed. Bronchoscopically, following the aspiration of pus at both sides, in the anterior segment and anterobasal segment on the right side, a purulent necrotic mass as a bronchial cast was seen. On the carinal mucosa of the upper left segmental bronchi, an infiltration was seen, and in the anterior segment a purulent necrotic mass that partially filled the bronchus was visualized. Histopathologically, in the material obtained from the anterior basilar bronchi at the right side, a fungal infection caused by the fungus *Aspergillus* was registered (differential diagnosis also included Mucormycosis) (Figure 1). The fungal infection was not confirmed microbiologically, and serological examination of the fungus confirmed the presence of antibodies to *Aspergillus* but not to the antigen (galactomannan). During this hospitalization the patient was, considering the probable fungal infection of the lungs, given a prolonged parenteral antifungal treatment with voriconazole.

Chest CT scan then showed, in addition to pneumotho
tax at the right side, a number of cavitations with fluid levels at both sides, as well as numerous nodular consolidations (Figure 2). In August the same year the patient was readmit
ted to the Institute for Pulmonary Diseases of Vojvodina for a histopathological verification of lung changes due to which open lung biopsy was indicated. At that time the patient complained of pain in the left hemithorax, productive cough and a fever of 38.5°C. At a follow-up CT scan of the thorax, the finding was worse in comparison to the previous one. Up to this admission to our hospital the patient had underwent two series of polychemotherapy in the following course: atrazine 3 days/cytosine + arabinoside 7 days. A video-assisted thoracoscopy was performed at the left side, along with a biopsy of the upper left lobe, and the slices of lung tissue in the area surrounding the organizing pneumonia contained necrotic detritus with rare necrotic fungi hyphae, while on the wall of small bronchi and bronchioles, as well as in their lumen, there was inflammatory infiltrate of lymphocytes, neutrophil granules, giant cells and numerous fungal hyphae that branch dichoto
mously at acute angles and correspond morphologically to *Aspergillus* (Figures 3). Hyphae were also present in the alveolar...
areas. Ziehl-Neelsen coloring revealed the absence of acid-alcohol resistant bacilli. The described histological picture corresponded to chronic necrotizing pulmonary aspergillosis which, in this case, developed as a complication of bone marrow aplasia phase.

Discussion

Aspergillus spp may cause a variety of pulmonary diseases, depending on the immune status and the presence of underlying lung disease. Rare manifestation of pulmonary aspergillosis is chronic necrotizing pulmonary aspergillosis, also called semi-invasive aspergillosis or subacute invasive aspergillosis which was first described by Gefter et al. 4 in 1981. and Binder et al. 3 in 1982. It is an indolent, cavitary and infectious process of the lung parenchyma usually caused by Aspergillus fumigatus.

CNPA usually affects middle-aged and elderly patients with an underlying chronic lung disease such as chronic obstructive lung disease, previous pulmonary tuberculosis, pneumoconiosis, cystic fibrosis, lung infarction, sarcoidosis, or less commonly patients underwent thoracic surgery and radiation therapy. It may also occur in mildly immunocompromised patients due to diabetes mellitus, chronic liver disease, malnutrition, connective tissue diseases (such as rheumatoid arthritis and ankylosing spondylitis), alcoholism and low-dose corticosteroid therapy.

Histologically, CNPA is characterized by necrosis of lung tissue followed by acute or chronic inflammation of the cavity wall and especially the presence of hyphae consistent with Aspergillus species. In contrast to invasive pulmonary aspergillosis, in CNPA vascular invasion and dissemination to other organs are unusual. 11 Denning 4 has proposed criteria for diagnosis of CNPA which include: clinical (chronic pulmonary or systemic symptoms including at least one of the following: weight loss, productive cough, hemoptysis), radiological (cavitary pulmonary lesions with evidence of paracavitary infiltrates, new cavity formation or expansion of cavity size over time) and laboratory criteria (elevated levels of inflammatory markers, isolation of Aspergillus spp. from pulmonary or pleural cavity or positive serum Aspergillus precipitin test) 12. This criteria could be helpful in the earlier diagnosis and therapy of CNPA and may improve the prognosis in patients with this condition.

Differential diagnosis of CNPA includes a great number of infectious diseases associated with lung cavities such as tuberculosis, actinomycosis, necrotizing pneumonias and lung abscesses caused by Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumonieae and Haemophilus influenzae and other fungal and parasite infections. Differential diagnostic problem could also be the presence of noninfectious diseases associated with lung cavities such as Wegener granulomatosis, metastatic disease in lung parenchyma which may also cavitate, sarcoidosis, lymphomatoïd granulomatosis, some primary tumors in the lung (lymphoma and Kaposi’s sarcoma, especially in HIV positive patients), Langerhans’ cell histiocytosis and autoimmune diseases (ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, primary amyloidosis) 13.

It may be difficult to distinguish CNPA from aspergillosis, especially if a previous chest X-ray is not available. However, in CNPA there is a local invasion of lung parenchyma and a pre-existing cavity is not needed, although a cavity with a fungal ball may develop in the lung as a secondary phenomenon, due to destruction caused by the fungus. On the other hand, in patients with AIDS who have aspergillosis, progression of aspergilloma over time was seen probably because it may invade the cavity wall and cause a local parenchymal destruction, in the same way as in patients with CNPA.

Antifungal therapy is the mainstay of treatment for patients with CNPA. Amphotericin B was initially used, but it proved to be relatively toxic so itraconazole became an effective alternative. More recently, voriconazole has emerged as a primary therapy for CNPA. Treatment is best evaluated by following clinical, radiological, serological and microbiological parameters. Surgical resection plays a minor role in the treatment of CNPA, being reserved for healthy young patients with focal disease and good pulmonary reserve, patients not tolerating antifungal therapy and patients with residual, localized but active disease despite the adequate antifungal therapy.

Conclusion

Because the yield of transbronchial biopsy specimens or percutaneous aspirates is relatively poor and thoracoscopic or open-lung biopsy is rarely performed in these patients, confirmation of the diagnosis is difficult and delayed diagnosis is common which may contribute to the morbidity and mortality associated with CNPA. However, a combination of characteristic clinical and radiological findings, histological demonstration of tissue invasion by fungus and either serological results positive for Aspergillus or the isolation of Aspergillus from respiratory samples are highly indicative of CNPA.

REFERENCES


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