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Combined Therapy with New Triazole Agent (Isovocunazole) and Micafungin in Invasive Pulmonary Aspergillosis Complicated by Hemoptysis in Immunocompetent Patient

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Abstract

Apergillosis in immunocompetent critical patients has increased incidence over the past two decades. Patients at risk include those with systemic steroid therapies and deteriorate pulmonary functions (COPD). Hemoptysis is a devastating complication of pulmonary aspergillosis reported in 28.9% of cases.

Keywords: Invasive pulmonary aspergillosis • Isovuconazole • Micafungin • Imaging

Introduction

Apergillosis in immunocompetent critical patients has increased incidence over the past two decades and can be found not only in severely immunocompromised patients with classical risk factors, but also in previously healthy patient. With normal immune function [1-3]. Patients at risk include critically ill patients in intensive care units, those with long course of systemic steroid therapies and deteriorate pulmonary functions (COPD) or prolonged chronic diseases (cirrhosis, tuberculosis etc.). Hemoptysis is a devastating complication of pulmonary aspergillosis reported in 28.9% of cases [4].

Case Report

A 76-year-old man was admitted to our Unit after seven days of pyrexia, productive cough and hemoptysis. His medical history was: 15-years COPD and steroid treatment, complete surgical resection and adjuvant radiotherapy of asymptomatic thymoma, decompensated heart disease with persistent atrial fibrillation, and HCV (CHC). Six weeks before the admission he suffered from bronchitis and a chest X-ray showed small nodule in the right superior lobe treated with levofloxacin for 10 days (Figure 1A). Radiographic signs of infiltration in the upper part of the right lung were found at Hospital admission (Figure 1B). A chest CT-revealed a 100 mm diameter cavitary mass complex in the upper lobe of the right lung, surrounded by nodules in both lungs (Figures 2A and 2B). Hemoptysis at admission was mild. Pulmonary tuberculosis was ruled out. Initial management included crystalloids, empiric antibiotics (piperacillin/tazobactam) as suspicion of pneumonia. Despite receiving 72 hours of intravenous antibiotics the fever increased. Blood *Aspergillus* galactomannan antigen was positive confirming evidence of invasive aspergillosis. *Aspergillus spp.* and *Candida albicans* was isolated from his endotracheal aspirate (Figures 3A and 3B). Antifungal triazole isavuconazole and the echinocandin micafungin were started [5]. His fever disappeared after three days. Unfortunately, massive hemoptysis occurred getting worse his cardiorespiratory system and deteriorated kidney function and patient died.

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Discussion

Invasive Pulmonary Aspergillosis (IPA) in immunocompetent patients is uncommon and occurs in those with chronic underlying disease rarely [6]. In immunocompetent patients, risk factors for *Aspergillus spp.* positive samples include the length of stay in critically patients, COPD, older age, ARDS, prolonged steroids use and chronic diseases (cirrhosis and inactive tubercular cavities) [7]. Complicated COPD and chronic asthma among colonized patients by *Aspergillus spp.* is described, although the distinction between IPA and *Aspergillus* colonization may be difficult in patients with previous pulmonary infiltrates. Blot, Taccone et al. [1] proposed alternative clinical algorithm to discriminate *Aspergillus* colonization from putative invasive pulmonary aspergillosis and current definitions of probable or possible IPA have been validated only in immunocompromised patients.

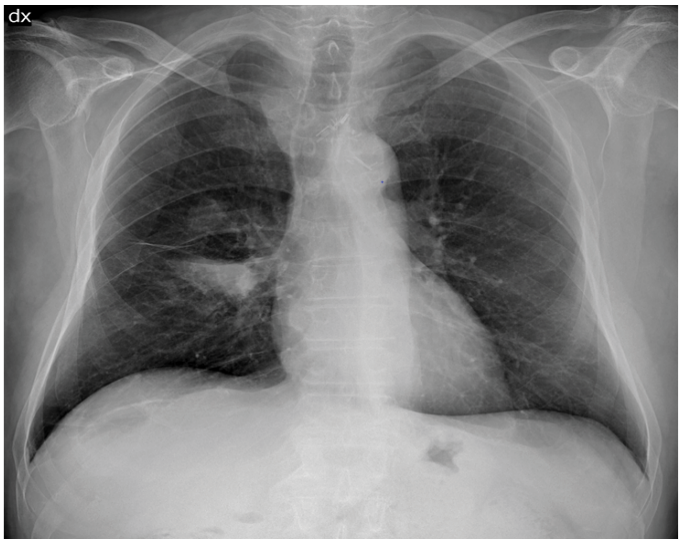

Figure 1A. Chest X-ray (6 weeks before Hospital admission): Suspicious cavitating lesion in the middle lobe, small nodule in the right superior lobe, no pathological findings in the left lung.

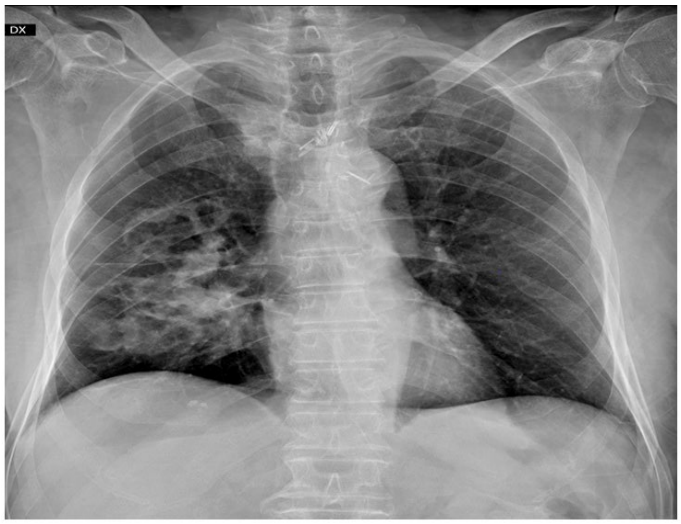

Figure 1B. Chest X-ray at hospital admission: Cavitation in the right superior lobe, irregular mass in the middle lobe, nodule in the left inferior lobe, no pleural effusion. Mediastinal surgical clips.

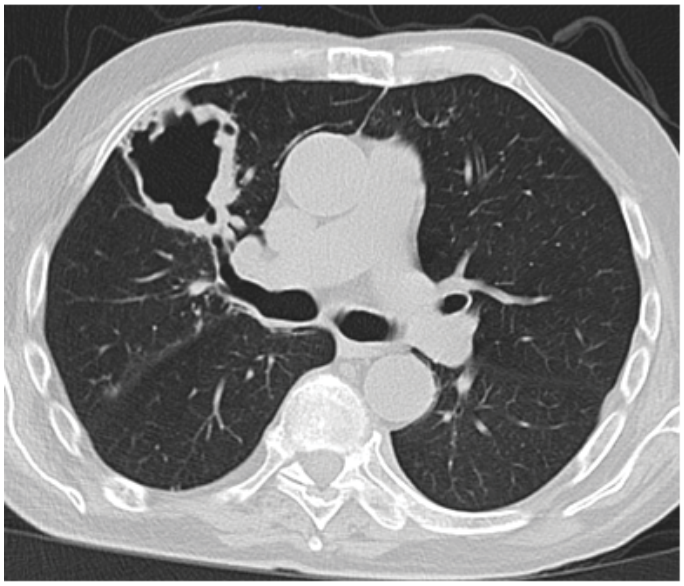

Figure 2A. Lung CT scan of pulmonary aspergillosis: Right upper lobe irregular, thick-walled cavitation with internal fronds.

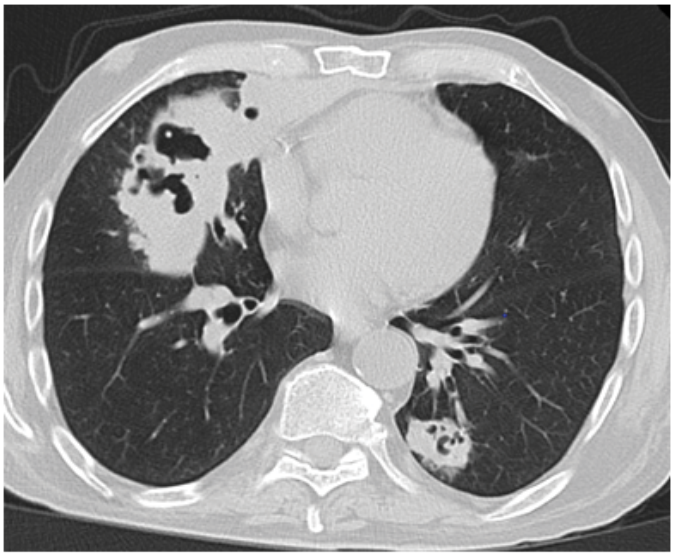

Figure 2B. Lung CT scan of pulmonary aspergillosis: Middle lobe cavitated consolidation and left-inferior lobe nodule with cavitation.

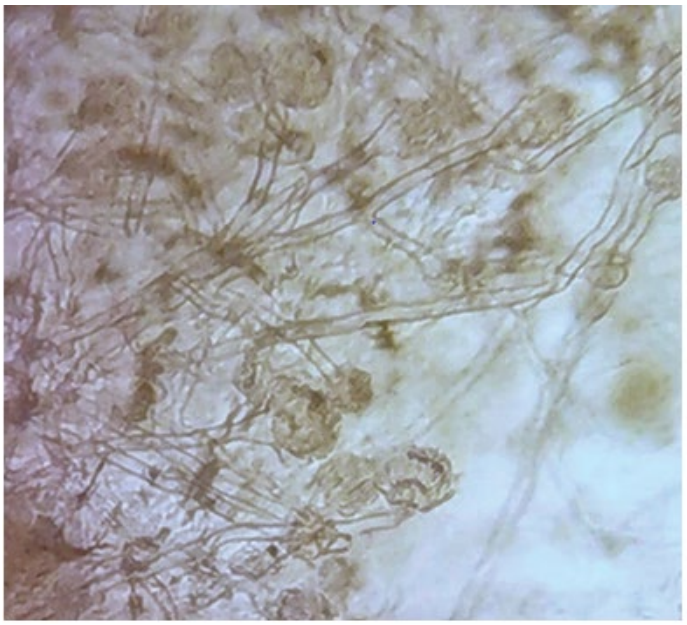

Figure 3A. The *Aspergillus* conidiophore with the typical and septate phialide-strains and spore: 10x magnification.

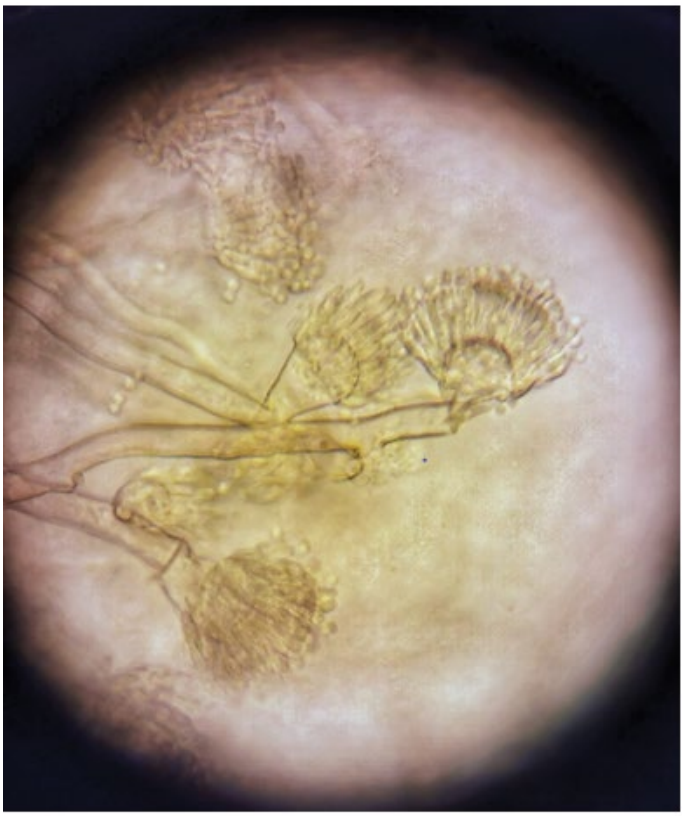

Figure 3B. Lung CT scan of pulmonary aspergillosis: 40x magnification.

We described a case of 76-old-man that showed symptoms and features of symptomatic obstructive aspergillosis, with cough, dyspnea, fever, and hemoptysis being the predominant complaints. The patient exhibited a high index of clinical suspicion, according with predisposing risk factors and his medical history. The cavitary mass complex revealed at CT scan was suggestive of IPA. According to the definitions for invasive fungal disease of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) [8], protocol diagnosis was made. IPA is categorized into proven, probable, and possible invasive fungal disease. A diagnosis of probable IPA in our patient was based on the presence of a combination of host factors and clinical features and positive mycology. The classification is

controversial in immunocompetent patient and the gold standard to diagnose IPA remains histopathology. The serum galactomannan was positive; although in the non-neutropenic setting galactomannan antigen detection on serum is of little value [9,10]. (Se and Negative Predictive Value-NPV- from 58% and 87%) and improves with ripetition of GM dosing, to 70% and 89% respectively. We met three diagnostic criteria of IPA defined as "probable" (EORTC criteria) and 4 diagnostic criteria defined as "putative IPA" in alternative clinical algorithm proposed by Blot, Taccone et al. [1] on the basis of surrogate markers of invasive fungal infection. The bronchoalveolar lavage showed *Candida albicans* and *Aspergillus spp.* Early we started antifungal therapy to our patient with highly suspected of IPA. There is no optimal therapy for IPA and mortality of invasive infections due to *Aspergillus spp.* is still high. Altough Voriconazole is primary treatment recommended with a dose of 4 mg/kg., we early started new therapy with Isovuconazole- isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily-SECURE TRIAL-) [11,12] and Micafungin 100 mg ev/ die, because of a synergistic interaction exhibited against *Aspergillus spp.* and simultaneous presence of candidiasis. The new triazole ISA in combination with echinocandin Micafungin (MFG) generated inhibition of ergosterol in the fungal membrane and B-glucan in the cell wall. Isovuconazole showed excellent water-solubility and relevant pharmacokinetics features and high oral bioavailability with a good safety [13]. The penetration into tissues is good. Other agents, such amphotericin B-liposomal or itraconazole, caspofungin, posaconazole and micafungin, can be considered for salvage therapy.

Conclusion

IPA occurs rarely in immunocompetent patients. In the elderly with underlying lung diseases and steroid treatment there is evidence that the *Aspergillus spp.* may be implicated in some cases. In our case the patient had relevant past medical history and the presence of *Aspergillus spp.* and *Candida albicans* isolated from endotracheal aspirate. Early diagnosis and aggressive treatment are associated with better outcome in patients with IPA14. We started promptly aggressive treatment with new triazole Isavocunazole and Micafungin and his fever disappeared after three days. However, the patient developed multi-organ failure and massive hemoptysis occurred and patient died.

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