Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Coinfection with Hypervirulent *Klebsiella pneumoniae* and *Aspergillus flavus* in a Critically Ill Patient with *Aspergillus* Overlap Syndrome: A Case Report

Yuansheng Xu, Yi Wang, Jinhong Wu, Xue Zhao, Ganying Huang, Jinyan Fang

Department of Emergency, Affiliated Hangzhou First People`s Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China

Correspondence: Jinyan Fang, Department of Emergency, Affiliated Hangzhou First People`s Hospital, Zhejiang University School of Medicine, No. 261 Huansha Road, Hangzhou, Zhejiang Province, 310006, People's Republic of China, Email fjy830818@126.com

Abstract: Pulmonary aspergillosis is generally categorized into three groups: allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis and invasive pulmonary aspergillosis. *Aspergillus* overlap syndromes (AOS) defined as the occurrence of more than one form of *aspergillus* disease in a single individual is not common. We present a 62-year-old-male patient with tachypnea, hypoxemia and shock after 4 weeks of cough, expectoration and intermittent hemoptysis, and 2 days of hyperpyrexia. Cardiac arrest occurring during tracheal intubation was resuscitated successfully. Laboratory examination showed acute kidney failure and severe myelosuppression with leukopenia and thrombocytopenia. Chest computed tomography (CT) scan showed the cavity with aspergilloma in the right upper lung lobe, a mass of consolidation in the right lower lung lobe and hyperdense shadow bronchiectasis in the left lower lobe. Bronchoscopy showed lots of sputum occluding the opening of the right airway bronchus. Laboratory examination showed significantly increased C-reactive protein (CRP) and procalcitonin concentration, serum (1,3)-β-D-glucan (BDG) and aspergillus immunoglobulin G (IgG) levels were also elevated. The metagenomic next-generation sequencing and sputum cultures revealed *Klebsiella pneumoniae* and *Aspergillus flavus* infection. Pulmonary aspergillosis, invasive aspergillosis infection and severe pneumonia were diagnosed. Initial caspofungin and meropenem followed by piperacillin-tazobactam sodium and voriconazole were administrated in combination. Continuous renal replacement therapy and mechanical ventilation were also performed. The patient's condition gradually recovered. Oral antifungal therapy was continued for 1 year after discharge and CT images gradually improved. Coinfections with *K. pneumoniae* and *A. flavus* in a patient with AOS will complicate clinical conditions. A search of PubMed showed few reports of similar cases. Clinicians should pay enough attention to the polymicrobial interactions and improve clinical management strategies, especially in critically ill patient with AOS.

Keywords: coinfection, *Aspergillus* overlap syndromes, *Klebsiella pneumoniae*, *Aspergillus flavus*, metagenomic next-generation sequencing

Introduction

Aspergillus is a ubiquitous fungus that causes a spectrum of pulmonary diseases ranging from noninvasive diseases to invasive infections. Allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA) are three main categories of pulmonary aspergillosis.[1] Sometimes, more than one form of aspergillosis coexists. Aspergillus overlap syndromes (AOS) refers to the occurrence of more than one form of aspergillus disease in a single individual. So far, few cases of AOS have been reported, and the specific incidence is unknown.[2] *A. flavus* is the second leading cause of invasive pulmonary aspergillosis after *A. fumigatus*, however, *A. flavus* rarely causes chronic cavitary aspergillosis or lung fungal balls.[1] Coinfections by bacteria, viruses, and fungi in the pulmonary cavity have been occasionally reported.[3–7] In this study, we present a critically ill AOS patient manifesting IPA and aspergilloma in a cavity and companying with hypervirulent *K. pneumoniae* (hvKP) infection.

Received: 19 October 2022
Accepted: 17 December 2022
Published: 29 December 2022

Coinfections complicate clinical conditions. To the best of our knowledge, this case is rather rare, which should raise concern among clinicians for the risk of such complicated coinfection.

Case Presentation

A 62-year-old-male patient was referred to our emergency department on August 24, 2020, after experiencing a 28-day history of cough, expectoration and intermittent hemoptysis without fever. He just received treatment of relieving cough and reducing sputum from the outpatient clinic until his symptoms worsened and were accompanied by chills and fever (highest temperature 39.0 °C) for 2 days and dyspnea for 1 day. He was diagnosed with pulmonary tuberculosis and was intensively treated with anti-tuberculosis drugs 10 years ago. He was never formally diagnosed with chronic obstructive lung disease despite a smoking history of about 20 pack-years. He was engaged in household waste recycling work but did not regularly wear a dust mask in the workplace.

On physical examination, he was tachypneic and had diffuse wet rales and low breath sounds in the right lung. His initial vital signs were 38.1 °C of body temperature, 130 beats/min of heart rate, 26 breaths/min of respiration rate, and 92/60 mmHg of blood pressure (norepinephrine maintained intravenously with the speed of 0.1ug/kg/min). Laboratory examination showed a white blood cell count of 900/mm^3, a neutrophil rate of 91.7%, platelet count of 17,000/mm^3, a creatinine concentration of 154.0 μmol/L, a CRP concentration of 259.39 mg/L, a procalcitonin concentration of >100 ng/mL, immunoglobulin E of 56 kIU/L, a CD^{4+} lymphocyte count of 39/μL, and a CD^{8+} lymphocyte count of 20/μL. Arterial blood gas analysis showed pH 7.32, PaO_2 59.6mmHg, $PaCO_2$ 29.7mmHg, HCO_3^- 15.4mmol/l, Lac 5.9 mmol/L, and oxygen saturation 92% (FiO_2 60%). He had negative real-time reverse-transcriptase polymerase chain reaction results for coronavirus disease 2019 (COVID-19) and influenza A and B. Ziehl-Neelsen staining of the sputum was negative for acid-fast bacilli.

Then his hypoxia symptoms progressed rapidly and the intubation was performed. However, cardiac arrest occurred during tracheal intubation. Spontaneous circulation returned after cardiopulmonary resuscitation for 15 minutes but frequent episodes of paroxysmal ventricular tachycardia remained. Amiodarone was also performed. We excluded cardiac tamponade by emergency bedside echocardiography, acute coronary syndrome was not considered for lack of dynamically changed electrocardiogram and serum cardiac troponin I level. Oxygen saturation could be maintained by positive pressure ventilation (Tidal volume 450mL, Fraction of inspiration oxygen 60%, Positive end-expiratory pressure 12cmH_2O, Respiratory rate 20/min). Computed tomography (CT) scan confirmed the presence of a thick-walled cavity in the posterior segment of the right upper lobe containing a 4.28cm*3.54cm soft tissue opacity attached to the cavity consistent with pulmonary aspergilloma and a mass of consolidation in the right lower lobe and patchy and nodule shadows in the left lower lobe (Figure 1A and B). Bronchiectasis and emphysema were also present. Bronchoscopic examination done under conscious sedation showed lots of sputum occluding the opening of the right airway bronchus. A biopsy of the right upper lobe B2 opening showed no cancer cells, though elevated serum squamous cell carcinoma-associated antigen level and enlarged mediastinal lymph nodes. Pulmonary aspergillosis and severe pneumonia were diagnosed. Caspofungin was empirically applied along with the antibiotic meropenem for decreased creatinine clearance of 43mL/min. Because of his acute kidney injury and anuria, continuous renal replacement therapy (CRRT) under regional citrate anticoagulation was also carried out. Subsequent serum BDG was 128.7 ng/L (0–100ng/L, Beijing Gold Mountainriver Tech Development Co. Ltd., China) and galactomannan (GM) was 0.05 (0–0.8, Bio-Rad Laboratories Shanghai Co., Ltd., China) on day 3. The aspergillus immunoglobulin G (IgG) levels was 172 AU/mL (0–35AU/mL). His sputum cultures also showed *K. pneumoniae* with a positive string test. Extended-spectrum beta-lactamase (ESBL) production was phenotypically confirmed using Clinical and Laboratory Standard Institute (CLSI) guidelines. The metagenomic next-generation sequencing (mNGS, performed by DIAN Diagnostics, China) of bronchoalveolar lavage fluid (BALF) revealed *K. pneumoniae* and *A. flavus* with reads of 3440 and 20, respectively. Meanwhile, the virulence genes iutA and rmpA2 as markers for hypervirulent pathotypes were present. The antimicrobial resistance gene SHV for ESBL was also detected. Antimicrobial susceptibility test showed that *K. pneumoniae* strains were susceptible to meropenem and piperacillin/tazobactam. Thus, invasive aspergillosis and hvKP coinfection were considered, the previous antibiotic treatment regimen was adopted unceasingly and clinical conditions gradually improved. The patient was weaned from CRRT on day 7 and from mechanical ventilation on day 10. Antimicrobials were also changed into piperacillin-tazobactam sodium (intravenously at 4.5g, q8h) on day 7 and voriconazole (orally at 0.2g, q12h) on day 10,

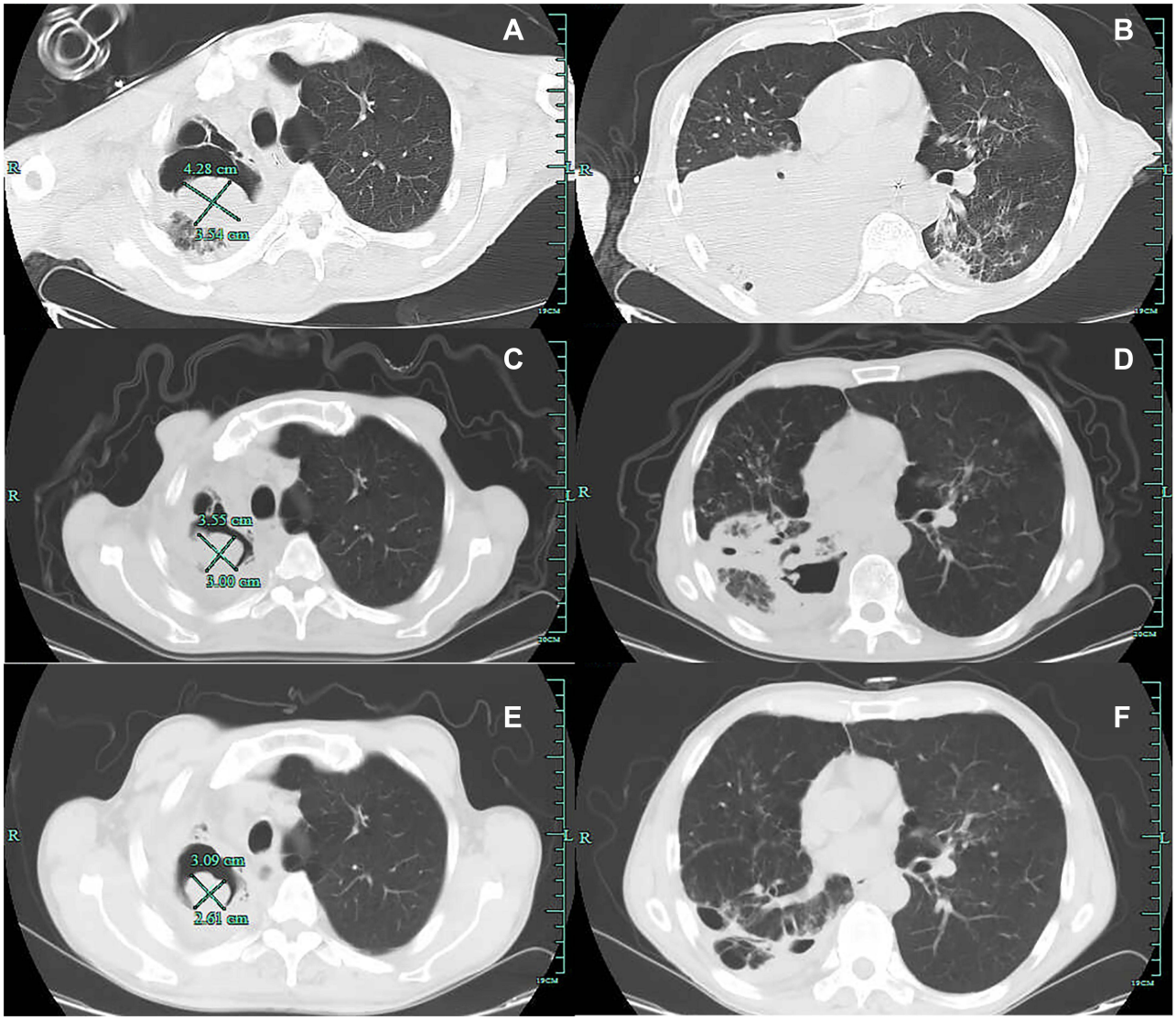

Figure 1 CT scan on admission (**A** and **B**), 2 months later (**C** and **D**) and 1 year later (**E** and **F**). (**A** and **B**) Axial CT images showed a thick-walled cavity in the right upper lobe containing a 4.28 cm*3.54 cm soft tissue opacity consistent with pulmonary aspergilloma and a mass of consolidation in the right lower lobe and patchy nodules shadows in the left lower lobe. (**C** and **D**) Axial CT images showed the fungal ball had been absorbed to 3.55 cm*3.00 cm and the clear left lower lobe, consolidation had been mostly absorbed. (**E** and **F**) Axial CT images showed the fungal ball had been further absorbed to a 3.09 cm*2.61 cm, and consolidation had been further absorbed.

whereas serum BDG and GM on day 10 rose to 231.3 ng/L and 5.50 respectively, then returned to normal until one month later. His BALF cultures on day 28 revealed *A. flavus* infection (Figure 2), whereas repeatedly negative of fungus before. The patient was discharged on day 48. Oral voriconazole therapy was continued for 1 year after discharge. Clinical symptoms and chest CT images gradually improved (Figure 1C–F). After more than one year of follow-up, the patient remained in good condition. The treatment process is shown in Figure 3.

Discussion

A. flavus is responsible for approximately 10% of bronchopulmonary infections. Inhalation of conidia from contaminated food, environmental and occupational exposure is the primary mode of transmission to humans. *A. flavus* can cause the same pulmonary lesions as *A. fumigatus* despite internal human milieu restriction of *A. flavus*.[8] Pulmonary aspergillosis is usually categorized into three groups: ABPA, CPA and IPA.[2] CPA usually occurs in normal immune hosts, while IPA is common in immunosuppressed hosts. The disease manifestation depends on the immune status of the patient as well as

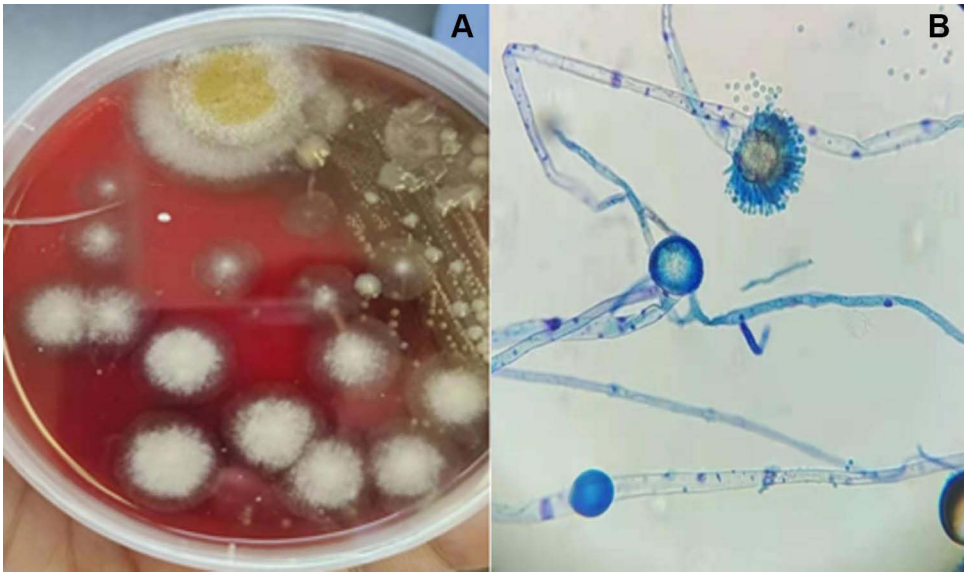

Figure 2 Macroscopic and microscopic features of *Aspergillus* flavus. (**A**) The BALF sample culturing on Columbia blood agar showed the yellow-green and cottony colonies. (**B**) Microscopic features including spiny conidiophores, radiant phialides on vesicles and biseriate phialides were observed under a light microscope using lactophenol cotton blue stain (LPCB, ×400).

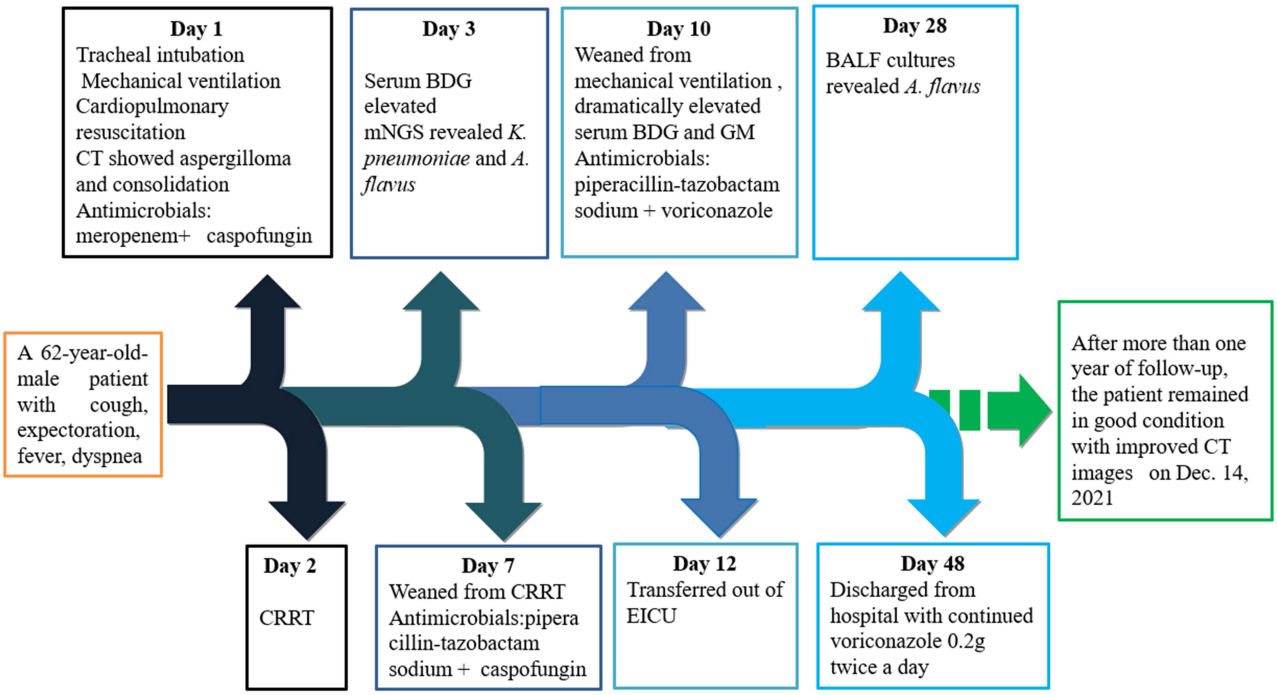

Figure 3 Treatment timeline of the reported case.

the structural integrity of the respiratory system. Sometimes, more than one form of aspergillosis coexists. AOS defined as the occurrence of more than one form in a single individual is increasingly being recognized.[2] It can emerge simultaneously or sequentially. The most common entity is the development of saprophytic aspergilloma (one form of CPA) in patients with ABPA or IPA. Usually, aspergilloma remains relatively stable in patients and rarely causes IPA.[9] The risk factors for IPA include neutropenia, defects in cell-mediated immunity, coinfection, chemotherapy, post-

transplant status, chronic granulomatous disease, hematologic malignancies, high-dose/long-term therapy, uncontrolled diabetes and so on.[1]

The histopathological examination is an important means to confirm the diagnosis of IPA. Although a biopsy of the right upper lung opening was performed in this case, no fungal hyphae was found by histopathology, we think it may be related to the biopsy location and inappropriate sampling. Low reads detected by mNGS and positive culture of *A. flavus* may also result from colonization or saprophyte. But even so, IPA was still suggested according to markedly elevated serum BDG and GM, positive aspergillus IgG and CT imaging findings. So, AOS was diagnosed based on the coexistence of aspergilloma and IPA. Several causes may contribute to AOS of aspergilloma and IPA. Firstly, old pulmonary tuberculosis can lead to the structural lesion of the airways and the lung parenchyma, which is the basis and premise for fungal infections. Bronchiectasis and other structural lung disease predispose the patient to *aspergillus* colonization and growth. Additionally, long history of smoking can also impair mucociliary clearance.

Secondly, serious infection resulting in leukopenia and low immune function is another factor. The significantly increased CRP and procalcitonin concentration and low white blood cell count were signs of serious bacterial infection other than simple fungi infection. The concentrations of both PCT and CRP in patients with bacterial infection are usually higher than those with single fungal infection.[10] This patient was otherwise healthy without any history of immunodeficiency, hematologic diseases and corticosteroid use. His leukopenia and suppressed cellular immune function were restored quickly one week later after the use of granulocyte colony-stimulating factor and antibiotic. The clinical data strongly supported the diagnosis of a severe outbreak of sepsis caused by hvKP, which is efficient at forming capsules, producing mucus and causing severe invasive multi-organ infection.[11] So far, there is no globally consistent definition for hvKP and its virulence level. A string test is the most common available laboratory method.[11] The positive string test with a viscous string >5 mm in length reflected a hypervirulent strain, which explained the aggressive progression of pulmonary infection and severe myelosuppression contributing to the occurrence of IPA. However, recent studies[12,13] have proved that not all hypermucous strains are hvKP, and not all hvKP strains are hypermucoviscous. The virulence genes such as rmpA, iroB, iucA, mrkD, entB, iutA, ybtS, kfu were strongly associated with hvKP, and demonstrated highly diagnostic accuracy for identifying hvKP strains.[12–14] The iutA and rmpA, the best-characterized virulence factors for hvKp[15] were also founded in our case.

Thirdly, viruses, bacteria and fungi generally coinhabit the airways with a dynamic composition as the immunity of the host progresses. Long-term usage of multiple broad-spectrum antibiotics can alter the local microbiologic flora. Undoubtedly, coinfection further complicates the clinical profiles, especially during the pandemic of COVID-19. Several studies had reported the occurrence of COVID-19 associated with IPA was 19.6–33.3% among patients requiring ICU admission.[5] In addition, IPA might comprise up to 17–29% of severe influenza patients and contribute to a high mortality rate of up to 67%.[16] Fortunately, multiple COVID-19 and influenza A and B tests of this patient were all negative. *Aspergillus* and *Cryptococcus* coinfection due to the existence of empty lung cavities was reported, despite being extremely rare.[7] *P. aeruginosa* are the most common bacteria present in structural lung disease, and coinfection with *A. fumigatus* usually results in a worse disease phenotype. *P. aeruginosa* secrets organic compounds to stimulate *A. fumigatus* growth, while *A. fumigatus* also stimulates *P. aeruginosa* production of cytotoxic elastase. Clinical cross-sectional data also indicated a worsened disease state in coinfected patients although also exhibiting mutually antagonistic facets.[4]

Nogueira et al[17] have demonstrated in vitro that *K. pneumoniae* can inhibit spore germination and hyphal growth and also impair the biofilm formation of *Aspergillus* species. Moreover, *K. pneumoniae* can also render *A. fumigatus* sensitive to cell wall stress and result in the upregulation of protective mechanisms, which involve remodeling and reinforcement of the fungal cell wall. Despite the demonstration of organism interactions in vitro, it remains unclear whether these interactions are clinically significant and how they promote disease progression. It also needs to be emphasized that the data in vitro may not necessarily be reflected by identical implications in vivo. In our case, we observed the temporary elevation of BDG and GM levels on day 10, it is unknown whether this change is due to those bacterial-fungal interactions or antibiotics-induced effect.

False-positive results of the GM caused by concurrent administration of piperacillin/tazobactam have been reported. But not all patients receiving this antibiotic will demonstrate circulating GM above the threshold considered positive for

invasive *Aspergillosis*. The clinical association of false-positive GM results during piperacillin/tazobactam treatment is small if a cut-off level of optical density index > 0.7 is used, and it also not systematic, while depending on the manufacturers.[18] Metan et al found that no significant interaction was observed between piperacillin/tazobactam administration and *Aspergillus* GM and BDG assays.[19] Two consecutive BDG levels ≧80 pg/mL will allow discrimination among invasive fungal infection and high-grade colonization.[20] This patient had typical aspergilloma and many risk factors including neutropenia, defects in cell-mediated immunity, coinfection, and structurally impaired lung. The cut-off levels of GM index > 0.8 and BDG > 100 pg/mL used in our laboratory were greater than 0.5 and 80 pg/mL respectively. So, we consider that the elevated BDG and GM levels are due to IPA rather than piperacillin/tazobactam effect.

Voriconazole is the first-line therapy for IPA. Echinocandins (such as micafungin and caspofungin) can be considered as alternative agent in high-risk neutropenic patient or salvage therapy after voriconazole.[21,22] We chose caspofungin as the initial antifungal agent for several reasons. After this patient`s spontaneous circulation returned, he still remained in a state of hemodynamic and electrical instability. Catecholamines such as norepinephrine and dobutamine were administered to maintain circulation stability for first few days. Amiodarone was also used to control paroxysmal ventricular tachycardia. Several studies have demonstrated the potential cardiotoxicity of voriconazole leading to prolongation of the QT interval and Torsade de pointes arrhythmia, and the combination of voriconazole and amiodarone may exacerbate this effect.[23–26] Meanwhile, this patient experienced acute kidney failure in a first week, so intravenous voriconazole is not appropriate for cyclodextrin solubilizing vehicle accumulation.[1] However, oral voriconazole did not guarantee an effective blood concentration for hemodynamic instability and unrecovered gastrointestinal function. In addition, this patient with neutropenia and severe immunosuppression had very high possibility of concomitant fungal infection except aspergillus, caspofungin can cover aspergillus, candida and other fungi. At last, synergistic interaction was detected between caspofungin and piperacillin-tazobactam in a neutropenic mice-invasive candidiasis model, but not between voriconazole and antibiotics yet.[27]

In fact, caspofungin was also shown to be effective in clinical response. After continuous antibacterial and antifungal therapy, the lung infection improved and the *aspergillus* ball has also been absorbed gradually. Therefore, clinicians must have a high index of suspicion for coinfection among critically ill patients, use multiple laboratory methods to identify coinfection and give combination therapy with full consideration of the patient's specific situation. However, the main limitation of the study was the absence of histopathological evidence of IPA.

Conclusion

Aspergillus may lead to different clinical manifestations, from allergic to invasive disease, depending on the patient's immune status and structural lung diseases. AOS is one of the typical cases. Moreover, sometimes more than one form of *aspergillus*-related lung disease coexists, along with the change of host immune status and the coinfection of other pathogens such as common *K. pneumoniae, P. aeruginosa, virus* and so on. The synergistic or antagonistic interactions between individual bacteria and fungi might be of clinical relevance. Undoubtedly, coinfection will complicate clinical conditions and result in worse clinical outcomes in comparison to infections with each of the pathogens individually. The clinician should take into account polymicrobial interactions to improve clinical management strategies.

Ethical Statement and Informed Consent

The study was approved by the Ethics Committee at the Hangzhou First People's Hospital of Zhejiang University. The patient provided written consent for the publication of this report.

Acknowledgments

The authors would like to thank Prof. Ye Jian for their valuable suggestions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; approved final version of the manuscript; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Zhejiang Provincial Traditional Chinese Medicine Science and Technology Project (Grant 2022ZB269). The Construction Fund of Medical Key Disciplines of Hangzhou (Grant OO20200485).

Disclosure

None of the authors has any conflict of interest.

References

1. Cadena J, Thompson GR 3rd, Patterson TF. Aspergillosis: epidemiology, diagnosis, and treatment. *Infect Dis Clin North Am*. 2021;35(2):415–434. doi:10.1016/j.idc.2021.03.008
2. Li L, Jiang Z, Shao C. Pulmonary aspergillus overlap syndromes. *Mycopathologia*. 2018;183(2):431–438. doi:10.1007/s11046-017-0212-y
3. Yue R, Wu X, Li T, et al. Early detection of legionella pneumophila and aspergillus by mNGS in a critically Ill patient with legionella pneumonia after extracorporeal membrane oxygenation treatment: case report and literature review. *Front Med*. 2021;8:686512. doi:10.3389/fmed.2021.686512
4. Keown K, Reid A, Moore JE, et al. Coinfection with Pseudomonas aeruginosa and Aspergillus fumigatus in cystic fibrosis. *Eur Respir Rev*. 2020;29(158):200011. doi:10.1183/16000617.0011-2020
5. Lai CC, Wang CY, Hsueh PR. Coinfections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect*. 2020;53(4):505–512. doi:10.1016/j.jmii.2020.05.013
6. Wang Q, Wang Z, Hao Y, et al. Coinfection with cryptococcus and aspergillus in an immunocompetent adult: a case report. *Medicine*. 2018;97(39):e12612. doi:10.1097/MD.0000000000012612
7. Enoki E, Maenishi O, Chikugo T, et al. Coinfection of Aspergillus and Cryptococcus in post-tuberculosis pulmonary cavity. *Pathol Int*. 2012;62:574–576. doi:10.1111/j.1440-1827.2012.02839.x
8. Krishnan S, Manavathu EK, Chandrasekar PH. Aspergillus flavus: an emerging non-fumigatus Aspergillus species of significance. *Mycoses*. 2009;52(3):206–222. doi:10.1111/j.1439-0507.2008.01642.x
9. Maturu VN, Agarwal R. Acute invasive pulmonary aspergillosis complicating allergic bronchopulmonary aspergillosis: case report and systematic review. *Mycopathologia*. 2015;180(3–4):209–215. doi:10.1007/s11046-015-9907-0
10. Tang JH, Gao DP, Zou PF. Comparison of serum PCT and CRP levels in patients infected by different pathogenic microorganisms: a systematic review and meta-analysis. *Braz J Med Biol Res*. 2018;51(7):e6783. doi:10.1590/1414-431x20176783
11. Shon AS, Bajwa RP, Russo TA. Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*: a new and dangerous breed. *Virulence*. 2013;4(2):107–118. doi:10.4161/viru.22718
12. Russo TA, Marr CM. Hypervirulent Klebsiella pneumoniae. *Clin Microbiol Rev*. 2019;32(3):e00001–e00019. doi:10.1128/CMR.00001-19
13. Russo TA, Olson R, Fang CT, et al. Identification of biomarkers for differentiation of hypervirulent Klebsiella pneumoniae from classical K. pneumoniae. *J Clin Microbiol*. 2018;56(9):e00776–e00818. doi:10.1128/JCM.00776-18
14. Yan Q, Zhou M, Zou M, et al. Hypervirulent Klebsiella pneumoniae induced ventilator-associated pneumonia in mechanically ventilated patients in China. *Eur J Clin Microbiol Infect Dis*. 2016;35(3):387–396. doi:10.1007/s10096-015-2551-2
15. Hwang JH, Hwang JH, Lee SY, et al. Prostatic abscess caused by Klebsiella pneumoniae: a 6-year single-center study. *J Clin Med*. 2022;11(9):2521. doi:10.3390/jcm11092521
16. Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: a literature review. *J Microbiol Immunol Infect*. 2021;54(1):46–53. doi:10.1016/j.jmii.2020.09.004
17. Nogueira MF, Pereira L, Jenull S, et al. *Klebsiella pneumoniae* prevents spore germination and hyphal development of Aspergillus species. *Sci Rep*. 2019;9(1):218. doi:10.1038/s41598-018-36524-8
18. Orlopp K, von Lilienfeld-Toal M, Marklein G, et al. False positivity of the Aspergillus galactomannan Platelia ELISA because of piperacillin/tazobactam treatment: does it represent a clinical problem? *J Antimicrob Chemother*. 2008;62(5):1109–1112. doi:10.1093/jac/dkn308
19. Metan G, Ağkuş C, Buldu H, et al. The interaction between piperacillin/tazobactam and assays for Aspergillus galactomannan and 1,3-beta-D-glucan in patients without risk factors for invasive fungal infections. *Infection*. 2010;38(3):217–221. doi:10.1007/s15010-010-0003-6
20. Martín-Mazuelos E, Loza A, Castro C, et al. β-D-Glucan and Candida albicans germ tube antibody in ICU patients with invasive candidiasis. *Intensive Care Med*. 2015;41(8):1424–1432. doi:10.1007/s00134-015-3922-y
21. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;63(4):e1–e60. doi:10.1093/cid/ciw326
22. Douglas AP, Smibert OC, Bajel A, et al. Australasian Antifungal Guidelines Steering Committee. Consensus guidelines for the diagnosis and management of invasive aspergillosis. 2021. *Intern Med J*. 2021;51(Suppl 7):143–176. doi:10.1111/imj.15591
23. Levine MT, Chandrasekar PH. Adverse effects of voriconazole: over a decade of use. *Clin Transplant*. 2016;30(11):1377–1386. doi:10.1111/ctr.12834
24. Elbey MA, Cil H, Onturk E, et al. QTc prolongation and torsade de pointes ventricular tachycardia in a small dose voriconazole therapy. *Eur Rev Med Pharmacol Sci*. 2012;16(1):100–102.
25. Alkan Y, Haefeli WE, Burhenne J, et al. Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis*. 2004;39(6):e49–e52. doi:10.1086/423275
26. Mourad A, Stiber JA, Perfect JR, et al. Real-world implications of QT prolongation in patients receiving voriconazole and amiodarone. *J Antimicrob Chemother*. 2019;74(1):228–233. doi:10.1093/jac/dky392
27. Keçeli SA, Willke A, Tamer GS, et al. Interaction between caspofungin or voriconazole and cefoperazone-sulbactam or piperacillin-tazobactam by in vitro and in vivo methods. *APMIS*. 2014;122(5):412–417. doi:10.1111/apm.12159