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CASE REPORT
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Rapid Progressive Antibiotic Resistant Pneumonia as a Challenging Case in Remote Area: Is it Antibiotic Resistant Bacteria or Fungal Infection?

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ABSTRACT

Introduction: Pneumonia is an acute inflammation of lung parenchymal due to pathogen infection (bacterial, viral, fungal, and parasitic) but not including specific parenchymal lung inflammation caused by *mycobacterium tuberculosis*. Fungal pneumonia is a rare disease and difficult to diagnose, this disease could lead to misdiagnosis with antibiotic resistant bacterial pneumonia.
Case Presentation: We present a 53 years old woman with comorbid hepatocellular carcinoma and low lymphocyte level who was suspected with fungal pneumonia and bacterial pneumonia as differential diagnosis who failed with adequate antibiotic regimen. We use fluconazole as a drug of choice due to lack of diagnostic tools to identify the causing microorganism, and limited source of medication.
Discussion: Fungal pneumonia is a rare disease and difficult to diagnose due to wide range of symptom. Presence of risk factor and inability to treat with antibiotic should be make a suspicion to fungal pneumonia. Radiograph finding of ground-glass opacity could help to make the diagnosis, followed with microbiologic examination. The treatment should be considered causative agent and patient conditions.
Conclusion: Antibiotic unresponsive pneumonia with risk factor, clinical and radiologic suggestive finding should be considered as fungal pneumonia as differential diagnosis, adequate treatment and examination including radiographic and microbiology should be performed.

INTRODUCTION

Pneumonia is an acute inflammation of the lung parenchymal due to pathogen infection (bacterial, viral, fungal, and parasitic) but not including specific parenchymal lung inflammation caused by *mycobacterium tuberculosis* (Kementerian Kesehatan Republik Indonesia, 2023). Pneumonia caused by fungal infection is rare compared to other infection agents, including bacterial and viral (Majdawati, 2021; Saragih et al., 2022). Due to multiple factors, the statistical data for fungal incidence in Indonesia is still limited. Still, an estimated 7.7 million Indonesians (2.89%) have a serious fungal infection each year, with pneumocystis pneumonia estimated at 15,400 in HIV and an equal number in non-HIV patients, and incidence of candidemia at 26,710 (Wahyuningsih et al., 2021). Fungal pneumonia is commonly undiagnosed in the early stage due to atypical symptoms, and the majority manifestation as asymptomatic infection with

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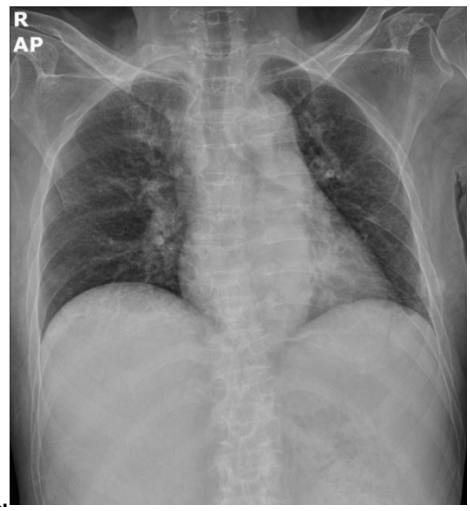
unresponsive antibiotic therapy; this condition could lead to misdiagnosis as antibiotic-resistant bacterial pneumonia(Majdawati, 2021). This could happen if not followed by good diagnostic stewardship that encompasses all stages of the clinical microbial diagnostic process and laboratory governance, including pre-analytical, analytical, and post-analytical stages. The pre-analytical stage includes the selection, handling, and transport of specimens. In this stage, collecting patient data is crucial, including clinical (signs, symptoms, clinical laboratory, radiology), demographic, and epidemiological that will be used in choosing the proper test and in the post-analytical stage. The analysis stage includes determining the quality of the specimen and the testing process. In contrast, the analytical stage includes reporting the result and interpretation according to the patient's condition, and the results are used by clinicians for patient management(Karuniawati, 2023; World Health Organization, 2016; Zakhour et al., 2023).

CASE PRESENTATION

A 53-year-old female patient who works as a housewife experienced complaints of shortness of breath after the 6th day of treatment at the hospital with a diagnosis from the emergency department of dyspeptic syndrome and hepatocellular carcinoma. The complaint of tightness was mainly felt, especially when lying down, and slightly reduced when the patient sat up. Patients also complain of fever on the second day after hospital admission, and it feels worse at night. The patient complained of coughing since the 3rd day of treatment; the patient denied coughing with phlegm, coughing up blood, and night sweats. Previously, the patient was admitted to inpatient care with heartburn due to dyspepsia syndrome with jaundice; the patient had a history of a diagnosis of hepatocellular carcinoma in previous years. General physical examination of the patient with blood pressure of 130/80 mmHg, pulse 84 times per minute, respiratory rate 32 times per minute, temperature of 39.5oC, and saturation of 97%. From the physical examination of the respiratory system, no abnormalities were found during inspection, palpation, or percussion. However, rough crackles were found throughout the lung fields. On abdominal examination, hepatomegaly measured two fingers below the costal arch. Blood laboratory results showed Hb 10.8 gr/dL, hematocrit 32.1%, leukocytes 16300/uL with a predominance of neutrophils 88%, platelets 400000/ul, white blood cell count showed eosinophil 1%, basophil 0,1%, Neutrophil 88%, lymphocyte 8.9%, and monocyte 2%. A radiological examination revealed a ground-glass opacity that experienced significant changes from the radiological image when the patient was admitted to the hospital. The patient was suspected of having fungal pneumonia, but a definitive examination using KOH fungal staining and sputum culture could not be performed due to hospital limitations. Based on the radiological findings, the patient was diagnosed with fungal pneumonia and bacterial pneumonia as a differential diagnosis that cannot be ruled out. Tuberculosis infection was ruled out due to negative results from molecular examination, and coinfection with HIV was ruled out due to negative results on the ELISA test. Viral infection was ruled out because this patient had no elevation of lymphocytes and monocytes.

a. 

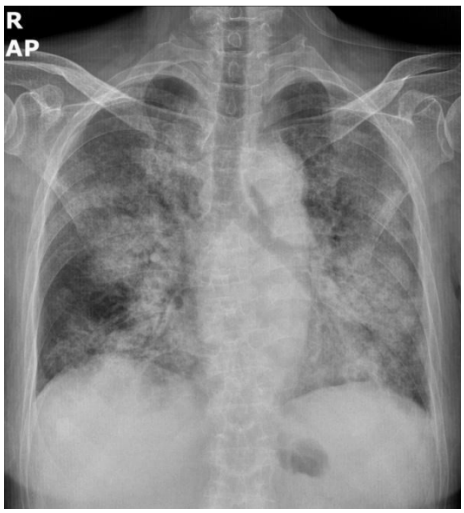
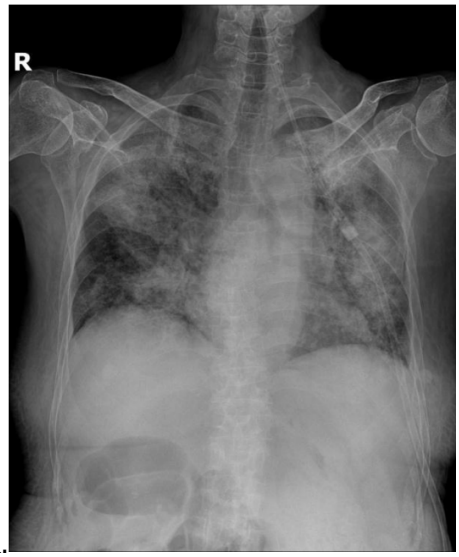
b. 

Figure 1. a. Chest X-ray of first-day hospitalization; b. Chest X-ray 6th day of hospitalization

The patient was given an additional antibiotic therapy of ceftriaxone 1gr/12 hours; due to no antimicrobial-resistant data in our facility, we commonly use ceftriaxone for bacterial pneumonia patients as empiric therapy. We give oral fluconazole to treat fungal infection with a loading dose of 300 mg on the first day after diagnosing pneumonia and continue with 150mg the next day for up to 10 days; this is caused by there is no intravenous fluconazole in our facility as it becomes the drug of choice for invasive coccidioidomycosis treatment. And there is no improvement in clinical and laboratory findings after 2 days of ceftriaxone. On the third day of admission of antibiotics, ceftriaxone is replaced by levofloxacin 750 mg daily, followed by metronidazole 500 mg three times daily. On the third day of administration of levofloxacin and metronidazole, no improvement was found in the patient's condition, either from laboratory results or clinical conditions; the patient's condition tended to worsen, with worsening breathing difficulties, worsening crackles, and fever still felt by the patient. On the fifth day of antibiotic admission, the antibiotic was changed to meropenem as the last option of antibiotic we have in our facility that we are not used, and fluconazole was planned to be continued for 21 days. After ten days of antibiotics and no improvement in the patient's condition, antibiotics were stopped, and bacterial pneumonia could be ruled out. The treatment was continued with supportive therapy and fluconazole. On the 19th day of fluconazole admission, the patient's condition improved; there was no fever, shortness of breath, or crackles. The patient could do daily activities without remarkable limitations and was ready to return home. The treatment of fluconazole was continued for 21 days.

a. 

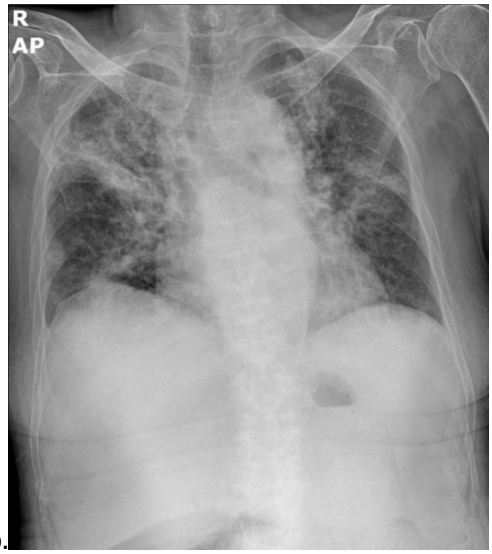
b. 

Figure 2. a. Chest X-ray after 10th day of hospitalization; b. Chest X-ray 21st day of hospitalization

DISCUSSION

Diagnosing fungal pneumonia is very difficult, and a range of manifestations, from asymptomatic to severe atypical symptoms, mimic other pulmonary infections that may be found in the patient. The suspicion of fungal pneumonia could be taken if there is a risk factor for fungal pneumonia followed by a history of fever > 40°C, mucopurulent phlegm sometimes accompanied by blood, shortness of breath, and symptoms of pneumonia don't relief with administration of adequate antibiotics (Majdawati, 2021). Some conditions that could become a risk factor for developing fungal pneumonia include neutropenia, hematological malignancies, hematopoietic stem cell transplant, COPD, solid organ cancer, hepatic cirrhosis, HIV infection, prolonged use of immunosuppressant including prolonged use of steroids (>7 days), prolonged ICU, near drowning, and post cardiac operation(Fortún, 2022; Wahyuningsih et al., 2021). In this case, the patient has hepatocellular carcinoma as a risk factor, and there is no improvement with adequate antibiotic treatment, making there a possibility of developing fungal pneumonia.

Chest X-rays, most commonly diagnostic tools in remote and limited source areas, could provide a more adequate diagnosis for the patient. Consolidation and ground-glass opacity/infiltration are commonly found in fungal pneumonia(Koesmarsono et al., 2022). In relation to that patchy or miliary infiltrate, linear and reticular opacities, homogenous round shape consolidation in the hilum region, and air cavities with "air sickle" nodules or nodules of various sizes could be found(Dermawan et al., 2018; Majdawati, 2021; Meena & Kumar, 2022). In this case, we found diffuse ground glass opacity predominantly in the middle to lower pulmonary segment followed by patchy infiltrate. Due to the similarity between tuberculosis and viral radiographic findings, we performed tubercular molecular examination and showed negative result for tuberculosis infection; the viral infection could be ruled out due to there being no elevation of monocytes and lymphocytes, which could be found generally in various viral infection such as influenza, EBV, cytomegalovirus, mumps, measles, adenovirus, coxsackie and rubella(Carrillo Holmes, 2024; Devi et al., 2022). The low level of lymphocyte count in this patient also becomes an indication that there is an immunosuppressive condition in this patient, which could lead to higher susceptibility to becoming infected by the microorganisms, including fungal infection, as lymphocytes have an essential role against microorganism infection(Bhattad, 2020; Doeleman et al., 2024; Warny et al., 2018).

Fungal pneumonia should be treated with adequate antifungal therapy based on causative fungus infection, severity of the disease, and clinical features of each patient. Voriconazole or Isavuconazole could be the first-line therapy for fungal pneumonia, especially for suspiciousness of aspergillosis infection before Amphotericin B, and most studies suggest the use of Voriconazole as a first-line therapy. Moderate to severe histoplasmosis must be treated with lipid Amphotericin B for 1-2 weeks, followed by Itraconazole for at least 12 weeks. Mild to moderate blastomycosis without CNS involvement can be treated with oral azole for 3-6 months, but with CNS involvement, it can be treated with lipid formulation Amphotericin B for 4-6 months, followed by oral azole for one year. In pulmonary coccidioidomycosis with mild disease, treatment is often unnecessary in regular hosts. Still, in severe pulmonary and extrapulmonary infection, triazoles (fluconazole and itraconazole) are the standard therapeutic agent; Amphotericin B could be used in the case that is refractory to triazole or in critically ill patients (Fortún, 2022; Lynch & Kontoyiannis, 2023; Susilo et al., 2023). Due to a lack of access to microbiology examination in our hospital, we cannot perform the microbiological examination on this patient; we use oral fluconazole as a drug of choice for this patient, in the presumption of majority causes of fungal pneumonia is Candida albicans (70%), followed by Aspergillosis (22%) and Mucormycosis (8%)(Majdawati, 2021). In our case, oral fluconazole improves the patient after nineteen days of antifungal administration.

CONCLUSION

In antibiotic-unresponsive pneumonia, fungal infection must be considered a causative agent, especially when risk factors, clinical signs, radiographic and microbiological examination suggest a fungal infection. Antifungal therapy should be started as soon as the diagnosis of fungal infection is made. Good anamnesis of risk factors, clinical signs, and radiographic imaging may help in limited source areas and the inability to access microbiological examination.

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