CASE REPORT

COVID-19 with melioidosis and cutaneous mucormycosis – A case report

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SUMMARY

It is generally known that the use of immunosuppressive therapy in COVID-19 infection gives rise to the occurrence of opportunistic infections. We reported a young, immunocompetent patient who presented with COVID-19 pneumonia and multiple erythema nodosum, a week post-trauma and was started on high-dose steroid therapy. Apart from the identification of *Burkholderia pseudomallei* in the blood culture, the skin culture and biopsy yielded *Saksenaea erythrospora*. Possibly compounded by a delay in diagnosis and therapy, the patient did not survive. We describe a COVID-19 pneumonia patient with concomitant melioidosis and cutaneous mucormycosis occurring opportunistically after corticosteroids, leading to an unfavourable outcome.

INTRODUCTION

The role of immunosuppressive therapy in treating severe COVID-19 pneumonia with hypoxia and hyperinflammation is well established,[1] but the treatment itself is well known to predispose patients to a wide range of opportunistic infections,[2] including melioidosis and mucormycosis. Mucormycosis, an angioinvasive fungal infection caused by filamentous fungi of the order Mucorales (Rhizopus (47%), Mucor (18%), Cunninghamella (7%), Saksenaea (5%), Rhizomucor (4%), Absidia (5%), and others (13%)), is a rare but deadly opportunistic infection. Whereas, melioidosis, as it is commonly known, is a tropical infectious disease caused by *B. pseudomallei*. Typically, these two pathogens are primarily transmitted via inhalation or direct contact with contaminated water and soil, especially percutaneous inoculation. Thus far, literature does not describe the coinfection of both organisms in an individual with COVID-19.

CASE PRESENTATION

A 27-year-old Malay man was found unconscious in the roadside drain and was intubated upon arrival at the nearest hospital. Further history from family members revealed that he had a history of recurrent seizures following traumatic brain injury in the past, without proper follow-up care. It was believed that he had a breakthrough seizure while riding a motorbike. Further history revealed that he had been unwell for a week with lethargy, irritability, and cough. He also inhaled narcotic substances. His rapid molecular COVID-19 test of naso-pharyngeal specimen detected SAR-CoV-2 virus.

On examination, there were abrasion wounds seen over his left arm and bilateral lower limbs. The Glasgow coma scale (GCS) was E1VTM1. Other physical findings were unremarkable. The baseline investigation results are described in Table I. In addition, the chest x-ray (CXR) revealed heterogeneous opacity involving multi-lobular areas in both lungs; and the contrasted cranial computed tomography (CT) revealed encephalomalacia over bifrontal areas, with no evidence of brain infection (Figure 1B and 1C). In light of severe COVID-19 pneumonia with presumed superimposed bacterial infection, he was administered intravenous steroid (an equivalent dose of 2mg/kg methylprednisolone) for a week, broad-spectrum antimicrobials (piperacillin/tazobactam), and anti-seizure medication (phenytoin). Anti-viral therapy was not considered as the illness had progressed to a hyperinflammatory state. After four days of hospitalisation, he had recovered from COVID-19 pneumonia and was then extubated with a full GCS.

However, two days later, he became restless and tachypnoeic. His condition subsequently deteriorated to septic shock and respiratory failure. In addition, for the first time, he developed painful, erythematous cutaneous nodules suggestive of erythema nodosum, over his bilateral forearms, legs and periumbilical area (Figure 1A), as well as bullous cellulitis over his left forearm. A skin biopsy was obtained (Figure 1E). The laboratory findings are described in Table 1. Repeated CXR showed patchy consolidation at right basal zone and the thoracic CT depicted grass-ground opacities involving right middle and lower lobe, along with cavitary pulmonary lesions and bronchiectasis at right lower lobe (Figure 1B and 1C). The antibiotic was upgraded to intravenous meropenem. However, he became increasingly septic and eventually succumbed to his illness.

Post-humus, his blood culture grew *Burkholderia pseudomallei,* confirmed by MALTI-TOF MS. The skin biopsy showed the findings of coagulative necrosis of fat lobules and stroma in the subcutaneous layer of skin, suggestive of panniculitis, along with fungal angioinvasion (Figure 1E) and the skin tissue culture grew mucormycosis (Figure 1D). The fungal PCR of the cutaneous tissue showed *Saksenaea erythrospora*.

This article was accepted: 14 May 2022
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Table I: Describes the serial laboratory results taken at different timeframes during the hospitalization. On the first day of hospitalization, the patient had raised septic markers, acute renal failure, transaminitis, and myositis. After four days of initial therapy, the biochemical parameters showed improvement. However, after a week of hospitalization, he developed sepsis with multi-organ failure

Day of admission / Laboratory	1 (baseline)	4	10
WCC (x10^9/L)	23.17	13.70	66.44
Hb (g/dL)	16.2	13.3	11.1
PLT (x109/L)	220	188	288
CRP (mg/dL)	22.9	16.4	30.8
Urea (mmol/L)	7.1	5.5	10.1
Creatinine (umol/L)	137	56	193
ALT (U/L)	144	120	117
ALB (g/L)	42	33	23
CK (U/L)	2116	1142	3206
Ferritin (ng/mL)	566	-	-
D-Dimer (ng/mL)	9499	-	-
PCT (ng/mL)	18.04	-	-

ALB, albumin; ALT, alanine transaminase; AMOX/CLAV, amoxycillin/clavulanic acid; BA, blood agar; CK, creatinine kinase; COVID-19, coronavirus disease; CRP, C-reactive protein; CT, computed tomography; EN, erythema nodusum; GCS, Glasgow coma scale; Hb, haemoglobin; LPCB, lactophenol cotton blue; MAC, MacConkey Agar; MALDI-TOF-MS, matrix-assisted laser desorption/ionization mass spectrometry; PAS, Periodic Acid-Schiff; PCR, polymerase chain reaction; PCT, procalcitonin; PLT, platelet; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDA, Sabouraud dextrose agar; TB, tuberculosis; TMP/SMX, trimethoprim/sulfamethoxazole; WCC, white blood cells.

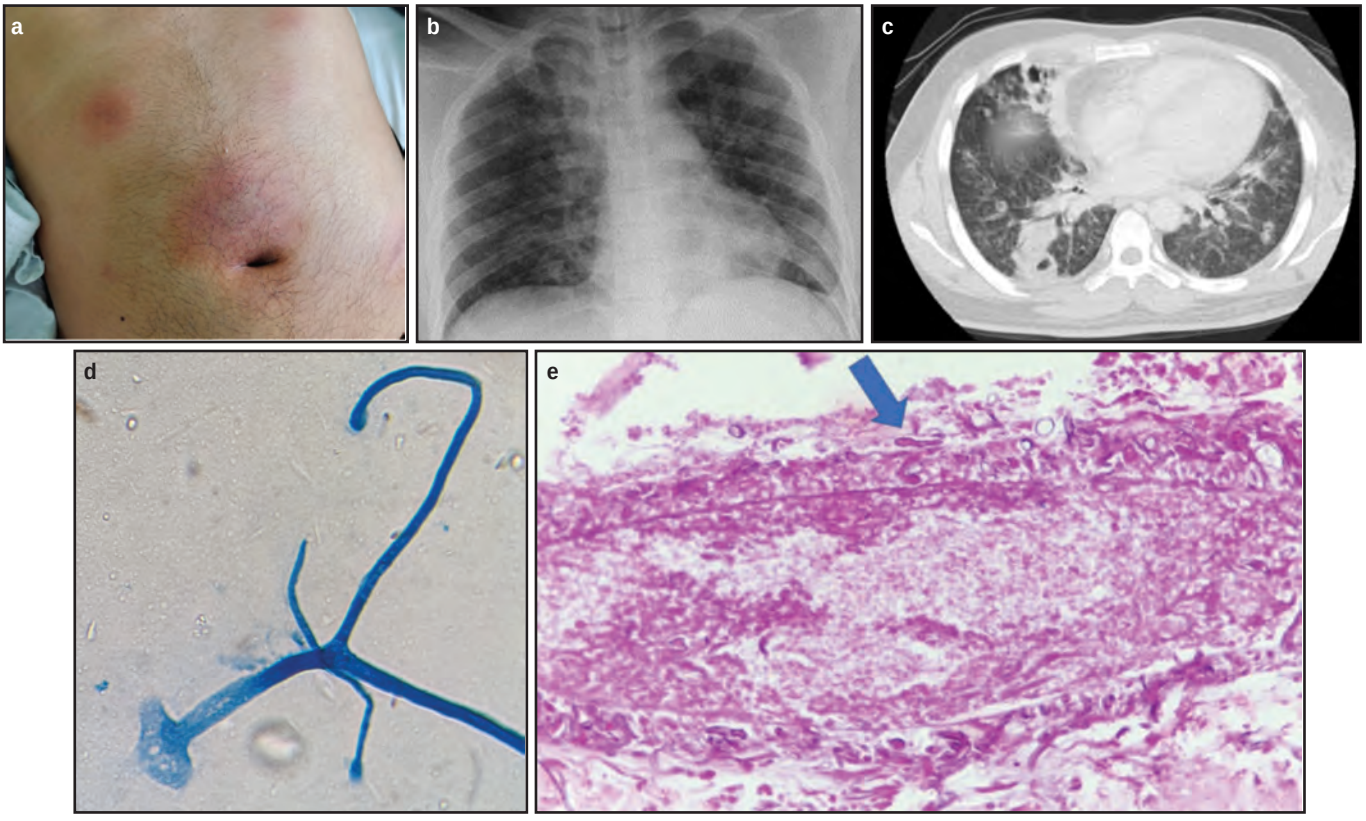

Fig. 1: Describes the clinical, radiological, microbiological, and histological findings in our case. Figure 1A depicts the clinical image of EN found at the anterior abdominal surface. Figure 1B describes the appearance of generalised heterogeneous opacity in the CXR taken at presentation. The image of thoracic CT (as shown in Figure 1C) shows the presence of heterogenous consolidation, tram-track opacities, and cavitations in bilateral lower lobes. Figure 1D shows the finding of fungal growth in skin culture, seen on SDA with LPCB staining, with the presence of a flask-shaped sporangiophore with columellae, suggestive of *Saksaneae sp.* Figure 1E describes the histopathological findings of skin biopsy taken from the left thigh and periumbilical area, with broad, non-septated, thin-walled hyphae detected within the blood vessel walls (shown with a blue arrow), stained with PAS stain

Neither fungal blood cultures nor fungal biomarkers were obtained. The TB workout was negative. The tracheal aspirate culture grew piperacillin/tazobactam-sensitive *Pseudomonas aeruginosa*. The complete diagnosis was revised to COVID-19 pneumonia with melioidiosis bacteraemia and cutaneous mucormycosis.

DISCUSSION

We report this unique case of infection due to two ubiquitous microorganisms that were most likely triggered by extensive immunosuppression using high-dosed steroid. Community-acquired co-infections along with COVID-19 infection are not uncommon.[3] In the background of COVID-19 pneumonia with concomitant coinfection and superinfection, a shorter course of low-dosed steroid, notably intravenous dexamethasone 6 mg daily for up to 10 days, should be considered when indicated.[1,4] In our case, given that he presented with severe hypoxia, it was difficult to distinguish COVID-19-related hyperinflammation from coinfection, and thus, a higher dose of steroid was administered to address the hyperinflammation. Of note, a prolonged use of high-dosed steroid, which is unproven in treating COVID-19 pneumonia, potentially promotes fungi and bacteria to thrive in vivo, leading to severe opportunistic infections.[5,6] The pathogenesis of opportunistic infection in the background of COVID-19 infection can be conceivably explained by immune dysregulation caused by immunosuppressive therapy or post-trauma endothelial injury.[7,8] Consistent with previous studies,[7,9] the risk factors contributing to both melioidosis and mucormycosis in our case include trauma and exposure to immunosuppressive agents used in treating COVID-19.

It was reported that the incidence of mucormycosis had substantially risen during the COVID-19 pandemic.[7,10] The genus Saksenaea, belonging to the class Zygomycetes, is often associated with rapid disease progression and angioinvasion commonly involving the lungs and rhino-cerebral areas.[7] It is traditionally characterised by the presence of flask-liked sporangia with columellae, non-septated sporangiophores, and rhizoids; tiny sporangiospores ranging from 3 to 11µm in diameter are contagiously spread via inhalation or cutaneous inoculation. Noteworthy, the presence of erythema nodosum is suggestive of a disseminated form of the disease.[11] In our case, the patient had probably acquired the disease from inhalation of droplets or spores from a contaminated environment during the time of trauma (he was found in a drain) or while inhaling narcotics. Additionally, direct inoculation from contaminated soil or water has also been described.[12] Fungal biomarkers including serum galactomannan and β-D-glucan are not useful for the diagnosis of mucormycosis, and hence, the tissue biopsy is essential. Diagnosis is confirmed by histopathology or fungal culture of the tissue specimen. Radiological findings of pulmonary mucormycosis (including cavitary lesions, consolidations, or nodules, reversed halo signs) can provide diagnostic clues to suspect mucormycosis. Amphotericin B and posaconazole are the drugs of choice in treating Saksenaea infection.[13] In our case, anti-fungal agent was not considered empirically as his clinical presentation was overshadowed by melioidosis.

Burkholderia pseudomallei, the causative agent of melioidosis, is an aerobic, non-sporulating, gram negative bacillus. With its soil-dwelling property, it is easily spread via skin inoculation and inhalation. Its clinical spectrum ranges from asymptomatic infection to fulminant disease involving multiple organs, including the pulmonary system. In our case, the patient presented with bacteraemia and severe pneumonia (described in Figure 1). Melioidosis pneumonia may mimic any forms of chronic granulomatous disease, including fungal infection, radiologically with diffuse nodular infiltrates, and cavities throughout bilateral lungs. The diagnosis of melioidosis is solely based on blood or tissue culture, with the appearance of grey-translucent colonies seen on BA and MAC. The use of MALDI-TOF MS helps in the rapid detection of melioidosis. Though not widely available, molecular investigation for *B. pseudomallei* may add value to the rapid diagnosis of melioidosis. Generally, the drug of choice during the intensive therapy for melioidosis is ceftazidime with carbapenems as an alternative, followed by the long-term oral eradication phase.

Owing to an atypical clinical presentations and challenges in phenotypic identification, establishing an appropriate diagnosis can be extremely challenging. Thus, it is essential to have a low threshold of suspicion for atypical organisms and to utilise multiple diagnostic tests in immunosuppressed patients to achieve a more rapid and holistic approach. While awaiting laboratory results, atypical imaging characteristics may facilitate the diagnosis of concomitant invasive mycoses or bacterial infection. Nevertheless, the granulomatous diseases, either mucormycosis or melioidosis, manifest with indistinguishable and non-specific imaging appearances, often triggering an extensive diagnostic workup. Furthermore, physicians should use immunosuppressive therapy judiciously in treating COVID-19 pneumonia.

DECLARATIONS

ETHICS APPROVAL

Approval of this study was obtained from the National Medical Research Register, Ministry of Health, Malaysia.

CONSENT FOR PUBLICATION

In consideration of having concerns about the possibilities of disease transmission on papers, an informed verbal consent was obtained from the guardian for publication

COMPETING INTERESTS

None to declare

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper. A special thank you is expressed to Dr Nor Arisah Misnan and Dr Tay Kim Heng for the patient management. In addition, we would also like to express special gratitude to the Department of Internal Medicine, Department of Infectious Disease, Department of Microbiology, and Department of

Radiology in Sungai Buloh Hospital, Selangor; and Department of Pathology in Selayang Hospital, Selayang, Malaysia.

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