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CASE REPORT

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Fatal disseminated mucormycosis associated with COVID-19

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Abstract

Secondary fungal infections are a critical problem that accompany immunosuppressive therapy for severe coronavirus disease 2019 (COVID-19). We report a fatal case of COVID-19 with disseminated mucormycosis diagnosed during autopsy. A 58-year-old man with diabetes was hospitalized for severe COVID-19 and treated with remdesivir, systemic steroids and tocilizumab. Following treatment, he was provided extracorporeal membrane oxygenation support. However, he died of multiple organ failure accompanied by pulmonary and kidney infarction, as revealed by computed tomography. Autopsy revealed that the infarction was caused by thromboangiitis due to mucormycosis in the brain, lungs, heart, liver and kidneys. Therefore, the diagnosis of disseminated mucormycosis was established. Disseminated mucormycosis is a rare complication of COVID-19. Although its early diagnosis is difficult, the disease progresses rapidly. Hence, we propose that immunosuppressive treatment for COVID-19 should be administered with caution considering the risk of developing severe opportunistic infections, such as mucormycosis.

KEYWORDS

autopsy, COVID-19, mucormycosis, thrombosis

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a worldwide problem. To prevent an excessive and uncontrollable immune response to the virus (so-called cytokine storm), anti-inflammatory therapies, such as systemic glucocorticoids or interleukin-6 (IL-6) antagonists, have been used, particularly in severe cases.[1] However, these immunosuppressive therapies and systemic organ damage caused by COVID-19 might result in secondary fungal infections, including pulmonary aspergillosis, candidiasis and, rarely, mucormycosis. We report a fatal case of severe COVID-19 with disseminated mucormycosis diagnosed during autopsy.

CASE REPORT

A 58-year-old man who had been on treatment for type 2 diabetes mellitus (DM) and hypertension was admitted to another hospital owing to acute respiratory failure caused by COVID-19. Before the onset of COVID-19, his height was 172 cm, body weight was 97.5 kg and body mass index was 32.9 kg/m^2. Despite combination therapy with steroid pulse therapy (methylprednisolone 1 g × 3 days), remdesivir and tocilizumab, followed by mechanical ventilation support, his respiratory failure gradually worsened. He was transferred to our hospital on day 6 after symptom onset. At admission, his oxygen saturation (SpO_2) was 90% under pressure-controlled ventilation (fraction of inhaled oxygen 1.0 and positive end expiratory pressure 6 cm H_2O). Blood biochemistry revealed a

severe inflammatory response (C-reactive protein 3.6 mg/dl), poor glycaemic control (HbA1c 8.6%), liver dysfunction (aspartate aminotransferase 82 IU/L, alanine aminotransferase 72 IU/L, lactate dehydrogenase 762 IU/L and γ-glutamyl trans peptidase 226 IU/L), pancreatic damage (amylase 1124 U/L) and acute kidney injury (blood urea nitrogen 90.6 mg/dl and Cr 3.85 mg/dl). Computed tomography (CT) revealed widespread ground-glass opacities and consolidations in bilateral lungs and pancreatic enlargement (Figure 1A–C). Repeated bacterial and fungal cultures of bronchial aspirates showed negative results. Venovenous extracorporeal membrane oxygenation was initiated on day 16. On day 29, left main pulmonary artery thromboembolism and right renal infarction had developed (Figure 1D,E). On day 34, right frontal lobe subcortical haemorrhage occurred (Figure 1F). On day 36, the patient eventually died of multiple organ failure and brain herniation.

Autopsy was performed 5 h after the patient's death. Macroscopically, both lungs were markedly oedematous and collapsed. Microscopically, extensive haemorrhagic infarction was discovered in both lungs. Pulmonary arteries, including the left main pulmonary artery, were obstructed with emboli comprising neutrophils and several fungal balls. The fungus had a thick, distorted mycelium, lacked bulkheads and had an irregular angle of branching, often >90°. Periodic acid-Schiff and Grocott staining of the fungal body revealed positive findings, suggesting that the fungus was *Mucor* (Figure 2A–C). Subsequent analysis of DNA extracted from the patient's lung identified *Rhizopus microsporus*. Outside the lungs, *Mucor* was observed in the heart, liver, right kidney, right adrenal gland and cerebellum, which resulted in thromboangiitis and infarction in these organs (Figure 2D–H). *Mucor* was also observed in the blood vessels of the bladder muscle layer and prostate, albeit without infarction. However, *Mucor* was not detected around the subcortical haemorrhage of the right frontal lobe. No evidence of embolisms caused by *Mucor* was observed in the spleen as well, although it showed widespread infarction. Autopsy findings suggested that the patient suffered from both multiple embolisms caused by *Mucor* and COVID-19-related coagulopathy. SARS-CoV-2 RNA was also not detected in any organs, including the lungs, heart, liver, kidneys, tongue, bone marrow, spine and brain, via reverse transcriptase-polymerase chain reaction.

DISCUSSION

During COVID-19, uncontrolled DM and systemic steroid treatments are significant risk factors for mucormycosis.[2] A recent report showed that tocilizumab, a humanized monoclonal antibody against IL-6 receptors, which had been proven to reduce the mortality of COVID-19, was also associated with a risk of secondary infection in patients with COVID-19. Therefore, clinicians should always be cautious for opportunistic fungal infections, including mucormycosis, in patients with severe COVID-19 who are treated with extensive immunosuppressive therapy. In addition, these immunosuppressive

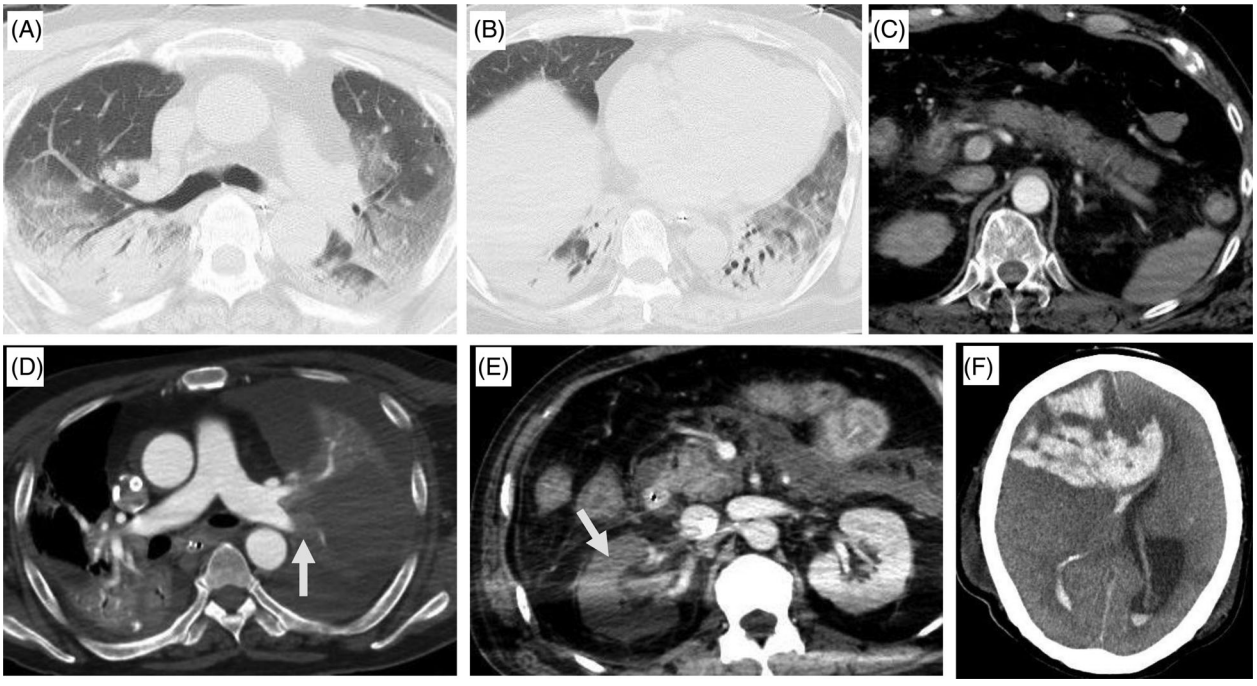

FIGURE 1 Serial computed tomography (CT) scans of the patient. Chest CT performed immediately after the transfer of the patient to our hospital showing bilateral consolidations, ground-glass opacities and atelectasis in lungs (A, B). Abdominal CT showing pancreatic enlargement (C). Severe pneumonia due to coronavirus disease 2019 (COVID-19) and secondary pancreatitis were identified. CT scan of the thorax and abdomen on day 29 showing complete atelectasis of the left lung and left pulmonary thromboembolism (arrow) (D), and right renal infarction (arrow) (E). CT scan of the head on day 34 showing subcortical haemorrhage in the right frontal lobe (F)

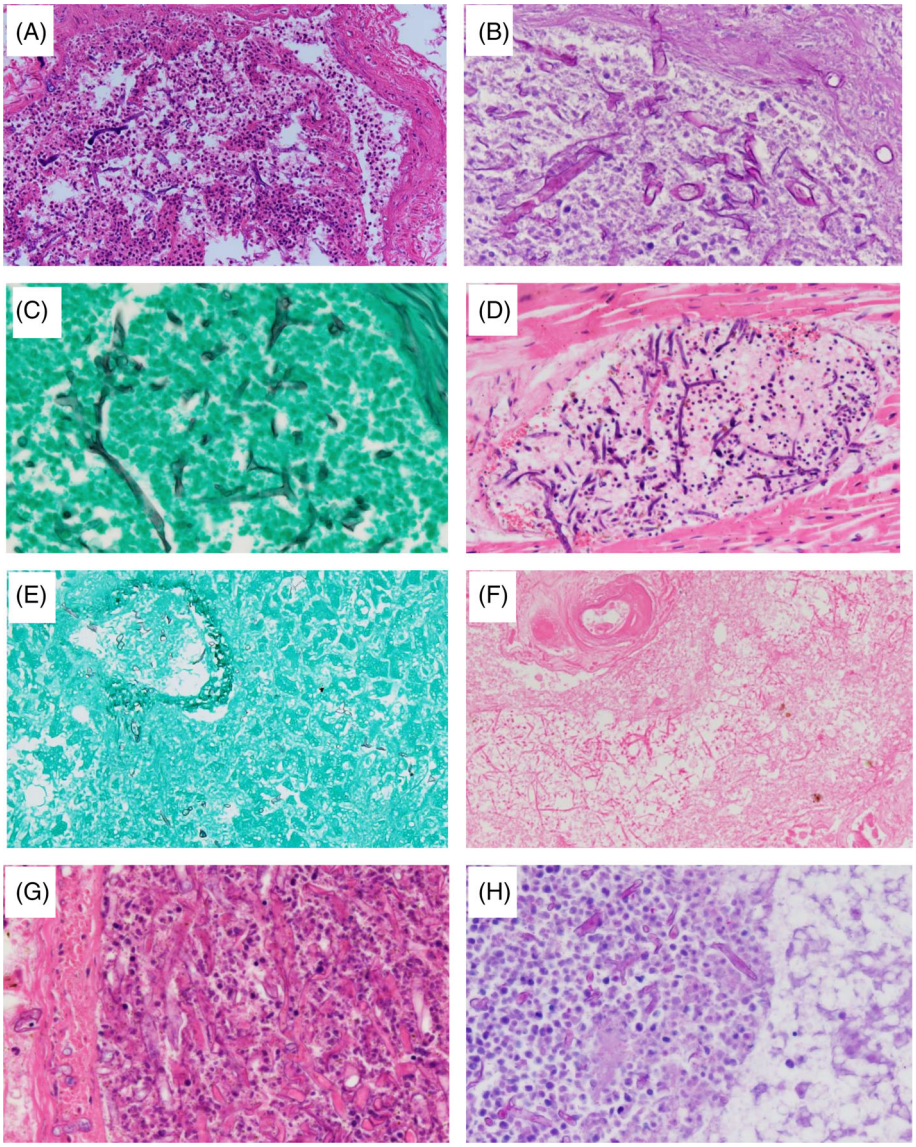

FIGURE 2 Microscopic findings of the autopsy showing dissemination and thromboangiitis in multiple organs due to *Mucor*. Pulmonary arteries were filled with thrombi comprising neutrophils and several *Mucor* fungus balls (haematoxylin–eosin staining) (A). *Mucor* stained with periodic acid-Schiff stain (B) and Grocott stain (C). *Mucor* infiltrated multiple organ blood vessels, including the heart (D), liver (Grocott stain) (E), right kidney (F), right adrenal grand (G) and cerebellum (H)

therapies should only be used for appropriately selected patients. It has been suggested that serum concentrations of IL-6 are not higher in COVID-19 than in other inflammatory diseases.[3] Hence, reliable biomarkers for selecting patients likely to benefit from strong immunosuppressive therapy should be established in future studies.

Thus far, most published articles on COVID-19-associated mucormycosis (CAM) have been reported from India or other South Asian countries, with only few reports from Japan. Along with the worldwide spread of COVID-19 and the induction of strong immunosuppressive therapies, the incidence of CAM has been increasing in other countries, including the United States, Brazil, Italy and United Kingdom.[4] Mucormycosis is difficult to diagnose during the early disease stages, but the disease often progresses rapidly.[2] Disseminated mucormycosis is also frequently diagnosed only during post-mortem analysis (majorly autopsy). Recent reports have suggested that the early detection of lesions through chest CT and lung biopsy, including transbronchial biopsy, could be useful for the early diagnosis of pulmonary mucormycosis. However, invasive biopsy can be difficult and even harmful for critically ill patients, such as those with severe COVID-19. Therefore, if an autopsy is not performed, mucormycosis might go undiagnosed. Nevertheless, in our patient, multiple massive embolisms (lungs and kidneys) had developed, which can be a crucial clue for suspecting mucormycosis considering that *Mucor* frequently invades blood vessels and is associated with embolism or infarction.[5] Nonetheless, because patients with COVID-19 in critical care are also

frequently diagnosed with thrombosis, it remains difficult to clinically distinguish mucormycosis-associated thrombosis from SARS-CoV-2-associated thrombosis. Hence, clinicians should consider the possibility of mucormycosis if the patient presents with sequential multiple thromboses.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Tomoya Horiguchi, Tetsuya Tsukamoto and Yoko Toyama prepared the data and drafted the manuscript. Toshiharu Sasaki, Tomoyuki Nakamura, Aki Sakurai, Naohide Kuriyama, Satoshi Komatsu, Eiko Sakurai, Arisa Tsuchimori and Seiji Yamada interpreted the data and revised the manuscript. Yoshiko Shigeyasu and Takuma Ina supported the data collection. Noriko Nakajima and Tadaki Suzuki contributed to the identification of *Rhizopus microsporus* and revised the manuscript. Kazuyoshi Imaizumi revised and edited the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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