



Case report

Mucor pulmonary embolism in a patient with myelodysplastic syndrome

T. Kakuwa^{a,*}, A. Ariga^{a,b}, J. Takasaki^a, M. Kato^c, T. Igari^c, Y. Shida^d, T. Okafuji^d,
S. Nakamura^{e,f}, Y. Miyazaki^e, H. Katano^g, M. Iikura^a, S. Izumi^a, H. Sugiyama^a

^a Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan

^b Department of Orthopedics, Tokyo Medical and Dental University, Tokyo, Japan

^c Department of Pathology, National Center for Global Health and Medicine, Tokyo, Japan

^d Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan

^e Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo, Japan

^f Department of Microbiology, Tokyo Medical University, Tokyo, Japan

^g Department of Pathology, National Institute of Infectious Diseases, Tokyo, Japan

ARTICLE INFO

Keywords:

Lung abscess
Mucormycosis
Myelodysplastic syndrome
Pulmonary infarction
Superinfection

ABSTRACT

Mucormycosis is a life-threatening infectious disease that occurs most commonly in immunocompromised patients such as those with hematological malignancies. Its clinical symptoms and associated radiological findings vary and specific biomarkers and culture characteristics have not been defined. An 85-year-old man who had been treated for myelodysplastic syndrome and tuberculosis for several months presented with subacute fever and worsening left-side chest pain. Contrast-enhanced computed tomography images depicted massive tumor-like consolidation without enhancement, expanding from the left lower lobe. Emboli that did not respond to anticoagulants were detected in the left descending pulmonary artery. Despite intensive treatment he developed multiple organ failure and died 47 days after hospitalization. Gross pathology of a lung autopsy specimen revealed left lower pulmonary arterial emboli and pulmonary infarction, which was concluded to be the direct cause of death. The emboli were histopathologically identified as invasive mycelia in vessels. *Mucor* sp. was detected via real-time polymerase chain reaction and immunohistopathological analyses revealed that the mold in the blood vessels of lung tissue was partially positive for the mucor antigen. In the present case of *Mucor* sp. pulmonary emboli in a patient with myelodysplastic syndrome, radiographic findings were hard to distinguish from those typical of a lung abscess.

1. Background

Mucormycosis is a life-threatening infectious disease that occurs most commonly in immunocompromised patients such as those with hematological malignancies [1]. Its clinical symptoms and associated radiological findings vary [2] and specific biomarkers and culture characteristics have not been defined. β -D glucan is reportedly not helpful [3]. The positivity rates of culture attempts from blood, sputum, bronchoalveolar lavage fluid, pleural effusion and nasal and paranasal discharge are low [4]. Histopathological analysis of biopsy specimens is necessary for a definitive diagnosis. Culture attempts are sometimes negative despite histopathological findings revealing *Mucor* sp [5]. Mucormycosis is known to invade vessels and is associated with embolism or infarction [6], which may be depicted on computed tomography

(CT) images. Herein we describe a case of *Mucor* sp. pulmonary embolism in a patient with myelodysplastic syndrome that was difficult to diagnose because of unusual radiographic image presentation.

2. Case report

The patient was an 85-year-old man who had undergone a total gastrectomy because of gastric cancer 8 years prior and had been diagnosed with myelodysplastic syndrome (RAEB-T, IPSS-IR 8.5 points) 2 years prior. He was categorized as “high risk” when considering hematopoietic stem cell transplantation, therefore azacitidine therapy had been continued. Six months before the current hospitalization he was diagnosed with pulmonary tuberculosis and administered rifampicin, isoniazid and ethambutol for 2 months, then switched to maintenance

* Corresponding author. Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655, Japan. Tel.: +813 3202 7181

E-mail address: tamaki.kakuwa@gmail.com (T. Kakuwa).

<https://doi.org/10.1016/j.rmcr.2020.101035>

Received 7 September 2019; Received in revised form 2 March 2020; Accepted 2 March 2020

Available online 3 March 2020

2213-0071/© 2020 The Authors.

Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

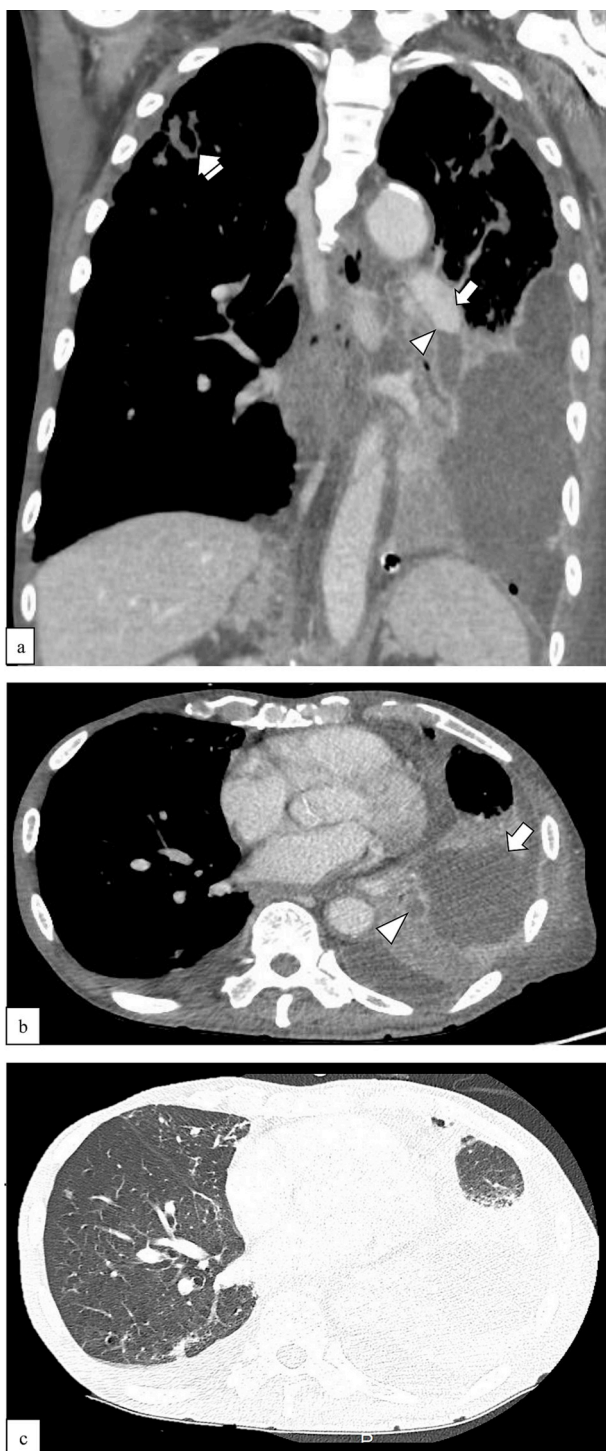


Fig. 1. Enhanced chest computed tomography (CT) images on the 21st day after admission. Pulmonary embolism of the left descending pulmonary artery was observed.

a. The arrow indicates the left anterior descending pulmonary artery and the arrowhead indicates the point where blood flow is interrupted by the embolus in the middle of the descending pulmonary artery. The separated arrow indicates a tuberculosis lesion in the right upper lobe.

b. The arrow indicates a wide homogenous poor-contrast region of the left lower lobe. The arrowhead indicates the left descending pulmonary artery filled with the embolus.

c. Ground-glass opacity, which is one of the typical CT finding in invasive fungal infection, was not observed in the pulmonary window setting.



Fig. 2. Macroscopic photograph of an axial slice of the left lung after formalin fixation. The arrow indicates a fungal mass filling the pulmonary artery.

therapy consisting of rifampicin and isoniazid. He developed thrombocytopenia due to myelodysplastic syndrome and rifampicin 4 months after treatment initiation. He was hospitalized with fever and left chest pain 5 months after treatment initiation and was diagnosed with aspiration pneumonia and pleuritis. Despite the administration of broad-spectrum antibiotics his symptoms deteriorated, in conjunction with gradually increasing oxygen demand. His sputum mycobacterial smear converted to positive, suggesting the possibility of tuberculosis recurrence.

Eleven days after the initiation of treatment contrast-enhanced chest CT revealed tumor-like consolidation without enhancement expanding from the left lower lobe, which was diagnosed as pulmonary abscess. He was treated with several broad-spectrum antibiotics including moxifloxacin in view of the possibility of *Citrobacter* and/or anaerobic bacteria. Acid-fast sputum culture collected 4 days before admission proved positive, prompting the addition of streptomycin to isoniazid to treat active pulmonary tuberculosis. When pleural effusion increased, a chest drainage tube was inserted into his left thorax in view of a possible empyema with fistula on hospitalization day 17.

His respiratory condition improved transiently after insertion of the chest drain tube, but fever and inflammation increased again a few days later. Contrast-enhanced chest CT on day 21 depicted massive tumor-like consolidation without enhancement expanding from the left lower lobe. Emboli were also detected in the left descending pulmonary artery (Fig. 1). Because he had developed disseminated intravascular coagulation and that was thought to be the cause of pulmonary embolism, anticoagulants were administered. They were discontinued 5 days thereafter however, due to hemoptysis.

On day 25, an exploratory puncture to the remaining abscess was performed. No pus was aspirated, but a small amount of bloody effusion was collected. *Enterococcus faecium* was cultured from the bloody clot, but no fungal species or mycobacteria were detected. Because the bacteria were repeatedly detected in sputum and pleural effusion and were thought to be the cause of the pulmonary abscess, vancomycin was administered. Despite intensive treatment he developed multiple organ failure and died 47 days after hospitalization.

Gross pathology of a lung autopsy specimen revealed left lower pulmonary arterial embolism (Fig. 2) and pulmonary infarction (Fig. 3). Acute myeloid leukemia with myelodysplasia-related changes was detected in the bone marrow. Histopathology of the necrotic lesion and the emboli revealed that mycelia had grown inside the mass and fungal emboli had spread from the pulmonary artery trunk over the left pulmonary artery proximal portion. The artery wall was destroyed by granulomatous inflammation and fungal invasion, which had also spread outside the artery. Pulmonary arterial embolism composed of invasive mycelia in conjunction with acute myeloid leukemia associated with myelodysplastic syndrome was deemed to be the direct cause of death. As well as the above, *E. faecium* was detected via necrotic lung tissue culture.

Real-time polymerase chain reaction (PCR) was performed to

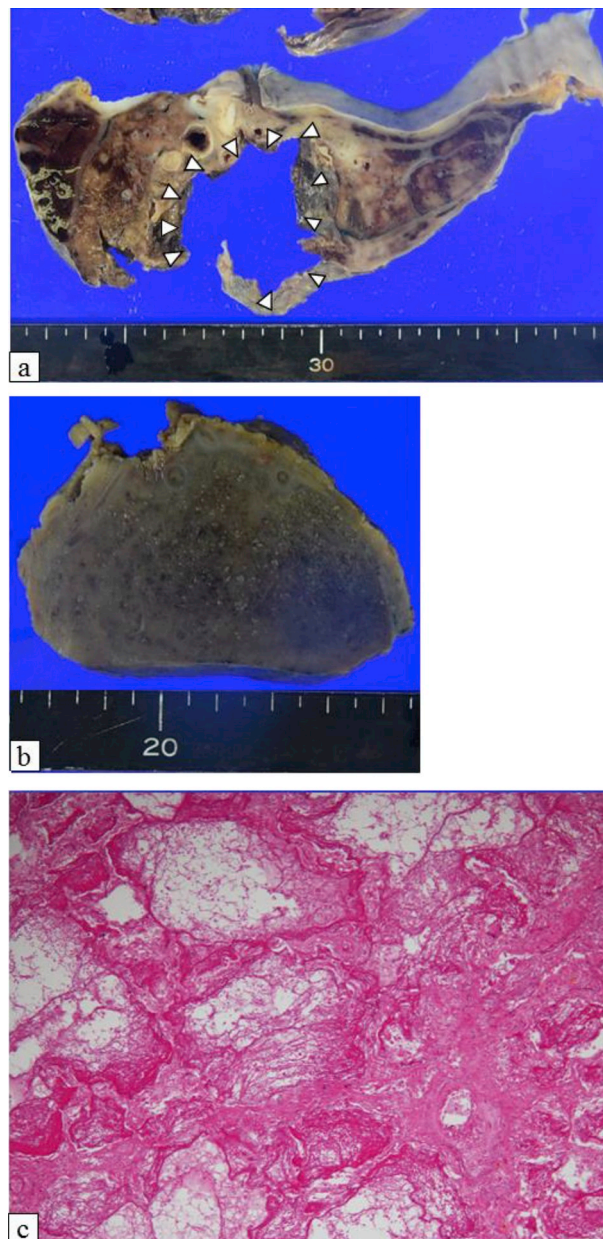


Fig. 3. Lung tissue after coagulation necrosis.

- a. Macroscopic photograph of a formalin-fixed lung slice depicting necrosis. The arrowheads indicates a missing section where a necrotic part of the lower lobe of the lung (shown below in “b”) dropped off.
- b. Macroscopic photograph of a necrotic part of the lung after formalin fixation. Most parts of the lung exhibited coagulation necrosis and only a little normal lung structure remained.
- c. Histological image of a necrotic part of the lung.

identify the species responsible for the mycosis. DNA was extracted from two samples cut from formalin-fixed paraffin-embedded specimens that had been obtained from a bacterial mass in a proximal portion of the pulmonary artery. A real-time PCR protocol designed to detect 15 types of fungi [7] identified *Mucor* sp. genes in the specimens. Immunohistochemistry using a mouse anti-*Rhizopus arrhizus* antibody (clone WSSA-RA-1; BioRad, New York, USA) as the primary antibody revealed that the mold in the blood vessels of lung tissue was partially positive for the mucor antigen (Fig. 4).

3. Discussion

In the present case there was massive pulmonary infarction at the end of the left descending pulmonary artery (Fig. 1). The lesion exhibited a round shape with rough and irregular edges, resembling an abscess [8], rather than a wedge-shape which is generally formed by the obstruction of a single pulmonary artery [9]. This rendered it difficult to make an accurate diagnosis. It was surmised that the mechanism of formation of the lesion did not involve the embolus drifting from a proximal pulmonary artery, but instead a substance in the bronchoalveolar region accumulated and invaded distal pulmonary vessels, ultimately forming the embolus.

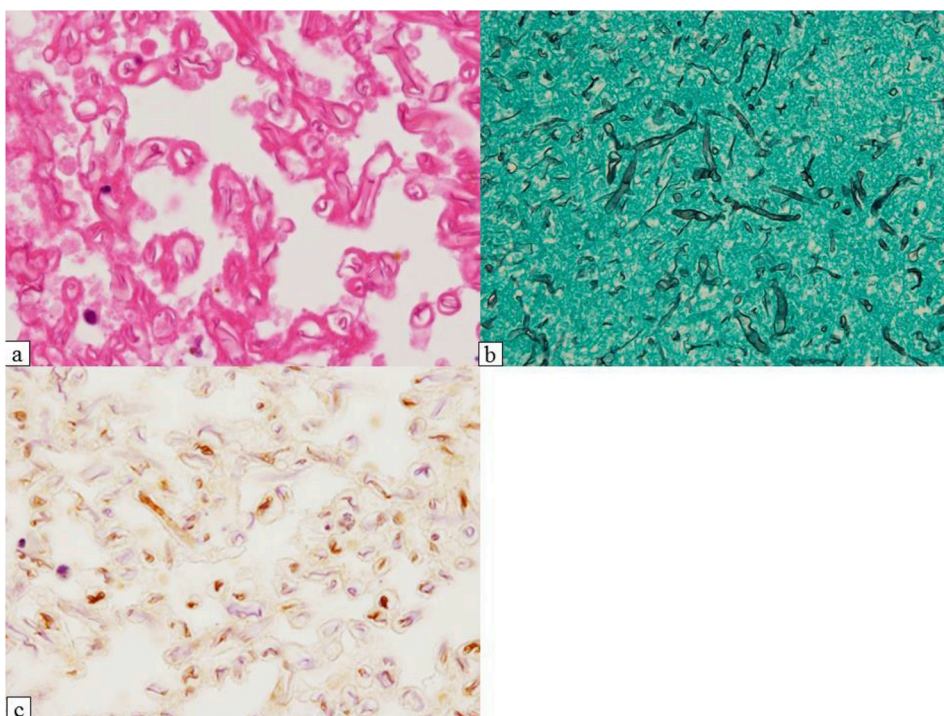


Fig. 4. Enlarged images of a necrotic part of the lung.

a. Hematoxylin and eosin-stained section depicting bacteria.

b. Grocott-stained section depicting slightly positive staining of bacteria.

c. Immunostaining with anti-*Mucor* antibody*.

*Mouse anti-*Rhizopus arrhizus* (MCA2577; Bio-Rad, New York, USA).

Pneumonia caused by a vasculotropic pathogen might at first only involve the invasion of capillaries or small peripheral vessels, but they may subsequently reach the pulmonary artery and trigger the development of an embolus. Considering the immunocompromised state caused by myelodysplastic syndrome, a pathogen that behaves in this manner can be assumed to be a fungal species, *i.e.*, *Aspergillus* sp. or *Mucor* sp. One point in time when other etiologies such as pulmonary infarction could have been suspected in the present case was when needle biopsy could not gather adequate pus-like specimens, despite CT images depicting an abscess-like area. Considering other diagnostic possibilities when faced with a clinical course that is not consistent with typical radiographic findings of pulmonary infarction or a clinical course of lung abscess may ultimately result in a definitive diagnosis.

Although percutaneous aspiration of the pulmonary lesions was attempted, pulmonary biopsy could not be conducted because of the risk of bleeding with thrombocytopenia. Filamentous fungi were detected via histopathology, mainly inside the pulmonary vessels, but it was difficult to detect fungi in sputum or via percutaneous aspirate culture. A transvascular approach such as right cardiac catheterization to obtain a histological sample, in addition to a percutaneous or transbronchial biopsy, may help to confirm a diagnosis of mucormycosis. Pulmonary endarterectomy, which is a common choice of treatment for chronic thromboembolic pulmonary hypertension [10], may be helpful.

Antifungal agents were not used in the present case, resulting in an untreated filamentous fungal disease killing the patient. There were several reasons why antifungal agents were not considered. Pulmonary *E. faecium* that was not well-controlled was detected via sputum culture and percutaneous lung aspirate, which led us to strongly suspect that it was the causative microorganism. Secondly, azole antifungals are incompatible with rifampicin [11], which the patient was administered to treat pulmonary tuberculosis. Furthermore, prophylactic antifungal agents were not necessary while following up his myelodysplastic syndrome. The results of autopsy revealed leukemic change, which may have worsened the patient's immunocompromised state. Finally, superinfection is always possible regardless of culture results, especially when the appropriate antibiotic subsequently proves to be inadequate.

4. Conclusion

We experienced a case of *Mucor* pulmonary embolism in a patient with myelodysplastic syndrome, in which radiographic findings were hard to distinguish from those typical of a lung abscess. When lung abscess accompanied by pulmonary embolism that is refractory to antibiotics is encountered, seronegative mucormycosis should be considered.

Acknowledgement

We thank Dr Owen Proudfoot from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

- [1] S. Brad, et al., *Mucormycosis: Principles and Practice of Transplant Infectious Diseases*, 2019, pp. 577–589.
- [2] M.H. Mark, et al., Pulmonary mucormycosis: radiological features at presentation and over time, *Am. J. Roentgenol.* 210 (2018) 742–747.
- [3] M.M. Francisco, et al., Role of (1→3)-β-D-glucan in the diagnosis of invasive aspergillosis, *Med. Mycol.* 47 (Supplement 1) (2009) S233–S240.
- [4] A. Abdollahi, et al., Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis, *Curr. Med. Mycol.* 2 (4) (2016) 15–23.
- [5] A. Charalampos, et al., *Mucormycosis: Diagnosis and Treatment of Fungal Infections*, 2015, pp. pp159–168.
- [6] E.L. Russell, et al., Epidemiology and treatment of mucormycosis, *Future Microbiol.* 8 (2013) 9.
- [7] H. Fukumoto, et al., Development of a new real-time PCR system for simultaneous detection of bacteria and fungi in pathological samples, *Int. J. Clin. Exp. Pathol.* 8 (11) (2015) 15479–15488.
- [8] M.W. Christopher, et al., Imaging pulmonary infection: classic signs and patterns, *Am. J. Roentgenol.* 202 (3) (2014) 479–492.
- [9] Latson, et al., Imaging of pulmonary infarction, *Clin. Pulm. Med.* 17 (6) (2010) 282–289.
- [10] K. Ishida, et al., Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension, *J. Thorac. Cardiovasc. Surg.* 144 (2012) 321–326.
- [11] Richard M. Tucker, et al., Interaction of azoles with rifampin, phenytoin, and carbamazepine: in vitro and clinical observations, *Clin. Infect. Dis.* 14 (1) (1992) 165–174.