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**Title:**

*Corynebacterium ulcerans* pneumonia treated with veno-venous extracorporeal membrane oxygenation: A case report

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**Highlights**

- Reports of *C.ulcerans* infection are increasing from companion animals.
- In pneumonia with pseudomembrane, *C. ulcerans* pneumonia should be suspected.
- V-V ECMO is necessary for airway obstruction due to *C. ulcerans* pneumonia.

**Abstract:**

We report the first case of airway obstruction due to toxin-producing *Corynebacterium ulcerans* (*C. ulcerans*) successfully managed with veno-venous extracorporeal membrane oxygenation (V-V ECMO). A 73-year-old woman living with companion animals was intubated for pneumonia of unknown origin and treated with an empirical antimicrobial agent. *Corynebacterium* species were detected in the sputum and treated as commensal bacteria. Subsequently, she suddenly could not ventilate owing to central airway obstruction caused by pseudomembrane formation. Therefore, V-V ECMO was initiated. Additional mass spectrometry identified the *Corynebacterium* species as *C. ulcerans*. Following treatment with antitoxin, she was successfully weaned from V-V ECMO. Hence, in patients in contact with companion animals who present with respiratory failure and pseudomembrane formation, *C.*

*ulcerans* pneumonia should be suspected and treated with antitoxin. *C. ulcerans* pneumonia may result in an inability to ventilate due to pseudomembrane formation. Therefore, treatment strategies including V-V ECMO should be considered in such cases.

**Keywords:**

*Corynebacterium ulcerans*, extracorporeal membrane oxygenation, pneumonia

**Introduction:**

*Corynebacterium* species detected in lower respiratory tract specimens are often treated as commensal bacteria (Zasada and Mosiej, 2018). Among the *Corynebacterium* species, *Corynebacterium ulcerans* (*C. ulcerans*), which produces diphtheria toxins, has attracted attention as a causative agent of zoonotic diseases (Wagner et al., 2010). In recent years, the number of cases of infection from companion animals has increased. Moreover, several fatal cases have been reported (Hatanaka et al., 2003; Otsuji et al., 2017; Tiwari et al., 2008; Wake et al., 2021). We report the first case of central airway obstruction due to toxin-producing *C. ulcerans* successfully managed with veno-venous extracorporeal membrane oxygenation (V-V ECMO).

**Case Report:**

A 73-year-old woman living with 17 domestic cats with no known medical or medication history presented with cough 2 days before hospital admission. She was rushed to her previous physician due to dyspnea and admitted to the hospital after being diagnosed with pneumonia of unknown origin. She received pazufloxacin and clindamycin treatment without showing any improvement. Therefore, the patient was intubated and transferred to our hospital for management of severe respiratory failure. On admission, the patient showed body temperature, 37.2°C; blood pressure, 110/ 73 mmHg; respiratory rate, 20 breaths/min; and percutaneous oxygen saturation, 89% (FiO<sub>2</sub> 1.0). Computed tomography predominantly revealed extensive infiltrative shadows in the dorsal left upper and lower lobes. Bronchoscopy showed pseudomembrane obstruction in the bronchus at the same location. The sputum culture showed *Corynebacterium* species. However, this species was considered unlikely to be an etiologic agent at that time. The patient was admitted to the intensive care unit and treated empirically with meropenem, levofloxacin, and prednisolone for severe bacterial pneumonia. Her respiratory status improved initially. However, on day 4 after hospitalization, she suddenly could not breathe, and V-V ECMO was initiated. Bronchoscopy revealed a pseudomembrane obstructing the trachea and main bronchi. Severe pneumonia caused by *C. ulcerans* was suspected based on the cat's breeding

history and findings of pseudomembrane formation. This was confirmed by mass spectrometry in the sputum collected on admission (Figure 1). *C. ulcerans* was susceptible to almost all antimicrobials except for clindamycin. Therefore, the prescribed empirical antimicrobials were switched to first-line azithromycin and continued for 14 days. Furthermore, administration of diphtheria antitoxin and prednisolone was discontinued. After long-term treatment, she was weaned from V-V ECMO on day 59 after hospitalization, weaned from mechanical ventilation on day 77, and transferred to another hospital for rehabilitation on day 120.

*C. ulcerans* isolated at our hospital was subjected to polymerase chain reaction analysis for the toxin gene and Vero cell cytotoxicity testing at the National Institute of Infectious Diseases for confirming toxin production. Although diphtheria immunization history was unknown, the patient's diphtheria antibody titer was 0.04 IU/mL and did not reach an adequate antibody titer of 1.0 IU/mL (Swart et al., 2016). In a later assessment, toxin-producing *C. ulcerans* was isolated from throat swabs of two indoor and two outdoor cats in her house.

### **Discussion:**

We encountered the case of a patient living with companion animals who experienced *C. ulcerans* pneumonia and was supported with V-V ECMO due to central airway

obstruction caused by pseudomembrane formation. This is the first report of successful management of severe pneumonia with central airway obstruction caused by *C. ulcerans* using V-V ECMO.

The pseudomembrane formation in the lower respiratory tract could be specific to *C. ulcerans* pneumonia, and is strongly suspected in patients in contact with companion animals. Furthermore, *C. ulcerans* synthesizes diphtheria toxin, which induces cell apoptosis and pseudomembrane formation (Sharma et al., 2019). Other potential diphtheria toxin producers comprise *Corynebacterium diphtheriae* and *Corynebacterium pseudotuberculosis*.

In our case, the patient's respiratory status improved with antimicrobial therapy. However, the pseudomembrane did not disappear. In addition, the patient could not breathe, leading to requiring urgent support with V-V ECMO. The pseudomembrane originated from the lobar bronchus level and then rapidly progressed to the main bronchus and trachea. The British guidelines recommend an early use of antitoxins and antimicrobial agents for treating *C. ulcerans* pneumonia (Begg N et al., 1994). Since *Corynebacterium* species detected in lower respiratory tract specimens are often treated as commensal bacteria, most isolates remain identified only at the genus level (Kawase et al., 2022). There may have been cases of inappropriate treatment due to missed

diagnosis of *C. ulcerans* pneumonia. The presence of pseudomembranes and a history of living with companion animals, *C. ulcerans* pneumonia should be kept in mind when treating patients with pneumonia.

*C. ulcerans* pneumonia can result in an inability to ventilate due to pseudomembrane formation with central airway obstruction. In our case, V-V ECMO was administered for central airway obstruction due to pseudomembrane formation. To date, the efficacy of V-V ECMO in severe pneumonia has not been demonstrated in a previous large multicenter collaborative study (Combes et al., 2018). Since our patient was diagnosed with severe pneumonia, V-V ECMO may not have been a good indication from this point of view. However, in terms of central airway obstruction, there are recommendations in the guidelines for extracorporeal life support systems. In addition, the use of V-V ECMO could be considered in cases of severe pneumonia with central airway obstruction (Tonna et al., 2021). In our case, the pseudomembrane was firmly adherent to the underlying tissue and took a long time to be removed because it bled easily when removed with dissecting forceps. The introduction of V-V ECMO would have been effective in resolving the inability to ventilate and supporting airway intervention. Hence, when *C. ulcerans* pneumonia is suspected, we should support patients with V-V ECMO or consider referral and transfer to a facility where V-V

ECMO can be performed.

The present case highlights two important points. First, when a patient in contact with companion animals presents with severe respiratory failure attributable to pseudomembrane formation in the lower respiratory tract, *C. ulcerans* pneumonia should be suspected, and early use of antitoxin administration should be considered. Second, since pseudomembrane formation with central airway obstruction by *C. ulcerans* can result in an inability to ventilate, treatment strategies, including V-V ECMO, should be considered.

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#### **Conflict of Interest:**

The authors declare that they have no conflicts of interest.

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**Ethical Statement:**

Informed consent was obtained from the patient's family for the publication of this case report and accompanying images.

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**Figure Legends:**

Figure 1. Radiological, endobronchial, pathology specimen, and sputum culture images.

(a) Chest radiography on admission. (b, c) Chest radiography and computed tomography image on day 4 of hospitalization show consolidations in the left lung field and atelectasis due to narrowing of the left main tracheal lumen. (d) Observation of the main bronchus on the second bronchoscopy. (e) The fragments of pseudomembrane sampled using forceps. (f) The colonies of *Corynebacterium ulcerans*.

