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ACUTE RESPIRATORY DISTRESS SYNDROME DUE TO MONKEYPOX VIRUS

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ABSTRACT

We report the first case of monkeypox virus (MPXV) associated acute respiratory distress syndrome (ARDS). A 34-year-old French woman with no medical history was admitted to the intensive care unit (ICU) for fever, altered mental status, hypotension and hypoxaemia. She presented with a diffuse skin rash with vesiculopustular lesions involving the four limbs and perineal ulcers with a skin swab positive for MPXV. On day 2, the patient presented moderate ARDS requiring invasive mechanical ventilation. She also had pleural empyema due to *Streptococcus pyogenes*. MPXV PCR was positive in the bronchoalveolar lavage, the pleural effusion and the blood. The patient was treated with tecovirimat. Despite the treatment, she had persistent viraemia for at least ten days. The patient condition rapidly improved; she was weaned from mechanical ventilation on day 18 despite the persistence of radiological lung opacities. She fully recovered and was discharged home on day 38 after admission.

KEYWORDS

Monkeypox virus, ARDS, viraemia, tecovirimat, skin rash

LEARNING POINTS

- This is the first case of monkeypox virus associated ARDS in a young woman with no medical history
- Biological follow-up showed disseminated MPXV and persistent viraemia
- Tecovirimat was well tolerated

INTRODUCTION

Human monkeypox (recently renamed mpox) is a zoonosis caused by monkeypox virus (MPXV)[1]. It was first reported in central Africa in 1970, where it is endemic. In May 2022, a series of cases was identified in Western Europe and then worldwide, corresponding to a new MPXV outbreak in non-endemic countries. By 5 January 2023 a total of 84,318 cases had been reported in 110 countries (83,127 in non-endemic

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countries)[2]. Almost all (98%) cases are men who have sex with men (MSM), typically with benign skin and genital lesions[3,4]. Life-threatening cases are rare: in recent times, the case fatality ratio has been around 3%–6% according to WHO reports[5], mostly occurring in young children and people with HIV in endemic countries[6–8]. At the time of writing, only 74 fatal cases had been reported during the recent outbreak (case fatality rate < 0.1%)[2].

CASE DESCRIPTION

We report the first case of documented ARDS related to mpox in a previously healthy 34-year-old French Caucasian woman admitted to the intensive care unit (ICU) for fever, altered mental status, hypotension, hypoxemia and a diffuse skin rash. Medical history was unremarkable apart from chronic tobacco and drinking habits. There was no history of recent travel out of France. Skin rash examination showed vesiculopustular lesions involving the four limbs, with perineal ulcers and a scab on an oedematous vulva.

METHODS

Herpes simplex virus (HSV), varicella zoster virus (VZV), and MPXV PCR testing (NeuMoDx™ 288 Molecular System – QIAGEN GmbH – differentiating MPXV clade I and II) were performed on swabs of skin lesions and revealed an MPXV infection due to West African clade (Clade 3)[9]. No other sexually transmitted disease was found after screening for HIV, syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

On the day of admission, investigation of the patient's hypoxaemia revealed loculated pleural effusion without lung anomaly on thoracic High-resolution CT (HRCT). The pleural fluid culture was positive for *Streptococcus pyogenes* with genetic toxin expression for streptococcal pyrogenic exotoxin B (SpeB) and streptococcal mitogen endotoxin Z (SMEZ).

Investigations for acute encephalopathy included a lumbar puncture revealing a clear cerebrospinal fluid (CSF), and normal cellularity and biochemistry. MPXV, HSV and VZV PCR were negative in CSF. A cerebral MRI and electroencephalogram showed no sign of encephalitis.

On day 2 the patient presented an acute respiratory failure with severe hypoxaemia requiring invasive mechanical ventilation, extensive bilateral condensation marked on the upper lobes on HRCT *(Fig. 1)* and normal echocardiography. These findings led to a diagnosis of moderate acute respiratory distress syndrome (ARDS) consistent with the Berlin definition[10]. Surprisingly, while no ulceration or vesicle was detected on bronchial endoscopy, the bronchoalveolar lavage (BAL) fluid was orange *(Fig. 2)* without obvious explanation (no rifampicin, jaundice, or sickle cell disease). On optical microscopy with May-Grünwald Giemsa stain *(Fig. 3)*, we observed a marked alveolitis (1,080,000 cells/mm^3) with 70% of non-altered neutrophils, 6% of lymphocytes and 24% of pigmented macrophages without any infectious agents. MPXV PCR was positive in BAL (cycle threshold C_t = 36) as in tracheal aspiration (Ct=34) with a higher viral load than blood (C_t = 38). It was also positive on pleural fluid, but negative on bronchial biopsies *(Table 1)*. The bacteriological culture of BAL fluid was sterile, and no respiratory virus was detected on bacterial and viral Multiplex PCR (kit FilmArray® Torch, RP2plus, bioMérieux). No cytopathogenic effect was observed on BAL fluid nor on bronchial biopsies. Histology of bronchial biopsies revealed alternating fibrous and oedematous territories, and discrete scattered lymphocytic inflammation.

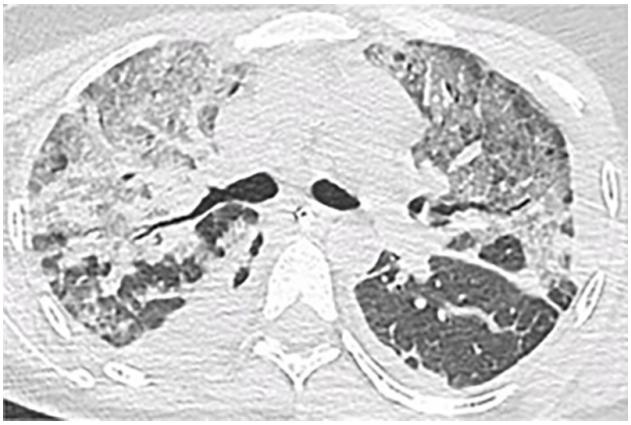

Figure 1. HRCT findings in monkeypox-related pneumonia

Figure 2. Macroscopic aspect of bronchoaveolar lavage fluid

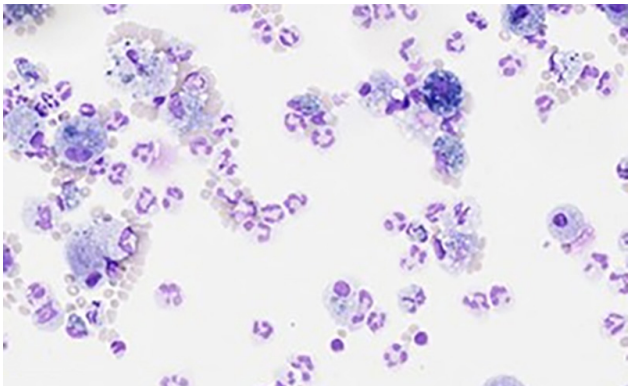

Figure 3. May-Grünwald Giemsa colouration on bronchoaveolar lavage fluid

	Day 1	Day 3	Day 5	Day 7	Day 11	Day 15	Day 17	Day 36
Pleural effusion	41	~	Not detected	39	~	~	Not detected	~
Plasma	~	38	38	38	39	~	~	Not detected
Bronchoalveolar lavage	~	36	~	~	~	~	~	~
Tracheal aspiration	~	~	34	35	37	36	~	~
Cerebro spinal fluid	~	Not detected	~	~	~	~	~	~
Urine	~	~	39	35	~	Not detected	~	~

Table 1. Summary of positive monkeypox virus PCR cycle threshold (C_t)

Empiric piperacillin-tazobactam with clindamycin and acyclovir were administered on admission. Acyclovir was stopped on day 2 after negative testing for HSV and VZV in cerebrospinal fluid. Tecovirimat, an antiviral agent supposed to have specific activity against orthopoxviruses[11], was started on day 3 for 14 days (600 mg twice a day) through a nasogastric tube[12]. No side effect was reported.

Respiratory condition rapidly improved on day 3, even before first administration of tecovirimat although pulmonary condensations and viraemia (C_t = 39) persisted on day 11. Vaccinia immune globulin intravenous was considered but ruled out, given the patient's improvement.

Immunological investigations revealed negative HIV serology, normal lymphocytes count on blood analysis and normal gamma globulin level. She also tested negative for neutralising autoantibodies against interferon alpha, beta and omega. The evolution was marked by a septic shock requiring a surgical drainage of pleural empyema due to Streptococcus pyogenes. Invasive mechanical ventilation was finally removed on day 18 after admission. The patient fully recovered and left the hospital on day 38 of hospital admission.

DISCUSSION

Here, we highlight the potential association between MPXV and ARDS, which has not been reported during the recent outbreak[13]. While bronchopneumonia and respiratory failure were described during previous outbreaks in endemic countries[14,15], ARDS has never been reported, likely due to limited investigations in low-resource settings. Although there is no evidence of a cytopathogenic effect, the temporal association of ARDS and higher MPXV load in respiratory samples than in blood suggests that the virus triggered or worsened a bronchopulmonary bacterial superinfection.

Life-threatening and lethal cases of MPXV infection usually occur in young children and people with HIV[6,7]. Here, we report a disseminated MPXV infection associated with ARDS in a young critically ill patient without any known immunodeficiency. There were no autoantibodies to type I IFNs and the patient's exome is still being studied.

Little data are available on the viral kinetics of MPXV infection because previous epidemics have occurred in resource-limited settings, and because in the current epidemic in Europe and the United States most cases are outpatients with no longitudinal follow-up. Here we observed prolonged viraemia and shedding of MPXV DNA in respiratory samples, as recently reported by Adler et al. in non-critically ill patients[16]. In this UK case series, one patient treated with tecovirimat had a shorter duration of viral shedding and illness compared to the other six patients. In our observation, the persistence and stability of viremia after 10 days of tecovirimat do not support a significant antiviral benefit even if it was well tolerated.

CONCLUSION

Our observation confirms that mpox may be associated with severe disease, particularly ARDS, even in the absence of known immunodeficiency.

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