CYTOMEGALOVIRUS CO-INFECTION COMPLICATING SEVERE PNEUMONIA IN A CRITICALLY ILL ELDERLY PATIENT WITHOUT CLASSICAL IMMUNOSUPPRESSION

Herikurniawan1*, Aziza Harris1

1Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital

ABSTRACT

Background: Cytomegalovirus (CMV) infection is typically associated with immunocompromised hosts; however, its role in critically ill patients without classical immunosuppression is increasingly recognized. In the setting of severe illness, factors such as systemic inflammation, immune dysregulation, and underlying comorbidities may predispose to opportunistic infections and viral reactivation. Aging-related immune dysfunction, or immunosenescence, may further contribute to this vulnerability in older adults.

Case Presentation: We report a case of an 82-year-old female with multiple comorbidities, including chronic kidney disease on hemodialysis, atrial fibrillation, heart failure, and diabetes mellitus, who was admitted with decreased level of consciousness. She subsequently developed acute respiratory failure due to severe pneumonia requiring intensive care and mechanical ventilation. Microbiological evaluation identified NDM-producing Klebsiella pneumoniae. Despite appropriate antibacterial therapy, the patient showed suboptimal clinical improvement, prompting additional evaluation. Subsequent investigation consistent with CMV reactivation, with a viral load of 4.75×10^3 IU/mL, consistent with viral reactivation. Laboratory findings demonstrated significant systemic inflammation, including elevated C-reactive protein (145 mg/L), procalcitonin (1.44 ng/mL), and leukocytosis. Following initiation of antiviral therapy, the patient demonstrated gradual clinical improvement with stabilization of respiratory status.

Conclusion: Elderly patients with multimorbidity may represent a functionally immunocompromised population. CMV should be considered as a potential co-infection in severe or non-resolving pneumonia in critically ill patients, particularly when the clinical course is prolonged or fails to respond to appropriate antimicrobial therapy. This case underscores the diagnostic challenge and clinical relevance of CMV reactivation in functionally immunocompromised elderly patients without classical immunosuppression.

Keywords: Cytomegalovirus; severe pneumonia; critically ill; elderly; immunosenescence; viral reactivation

ABSTRAK

Latar Belakang: Infeksi Cytomegalovirus (CMV) umumnya dikaitkan dengan pasien dengan kondisi imunokompromais; namun, perannya pada pasien sakit kritis tanpa imunosupresi klasik semakin banyak dikenali. Dalam kondisi penyakit berat, faktor-faktor seperti inflamasi sistemik, disregulasi imun, serta komorbiditas yang mendasari dapat meningkatkan kerentanan terhadap infeksi oportunistik dan reaktivasi virus. Disfungsi sistem imun terkait penuaan, atau imunosenescence, dapat semakin berkontribusi terhadap kerentanan ini pada populasi usia lanjut.

Laporan Kasus: Kami melaporkan kasus seorang perempuan berusia 82 tahun dengan berbagai komorbid, termasuk penyakit ginjal kronik yang menjalani hemodialisis, fibrilasi atrium, gagal jantung, dan diabetes melitus, yang dirawat dengan penurunan kesadaran. Pasien kemudian mengalami gagal napas akut akibat pneumonia berat yang memerlukan perawatan intensif dan ventilasi mekanik. Evaluasi mikrobiologi mengidentifikasi Klebsiella pneumoniae penghasil NDM. Meskipun telah diberikan terapi antibakteri yang adekuat, perbaikan klinis tidak optimal sehingga dilakukan evaluasi lanjutan. Pemeriksaan lanjutan mengonfirmasi adanya infeksi Cytomegalovirus (CMV) dengan viral load sebesar $4,75 \times 10^3$ IU/mL, yang konsisten dengan reaktivasi virus. Temuan laboratorium menunjukkan inflamasi sistemik yang signifikan, termasuk peningkatan kadar C-reactive protein (145 mg/L), prokalsitonin (1,44 ng/mL), dan leukositosis. Setelah pemberian terapi antivirus, pasien menunjukkan perbaikan klinis bertahap dengan stabilisasi kondisi respirasi.

Kesimpulan: Pasien usia lanjut dengan multimorbiditas dapat merepresentasikan populasi dengan kondisi imunokompromais fungsional. CMV perlu dipertimbangkan sebagai kemungkinan koinfeksi pada pneumonia berat atau yang tidak membaik pada pasien sakit kritis, terutama apabila perjalanan klinis berkepanjangan atau tidak respons terhadap terapi antimikroba yang adekuat.

Kata kunci: Cytomegalovirus; pneumonia berat; pasien kritis; lansia; imunosenescence; reaktivasi virus

Correspondence : Herikurniawan
Division of Pulmonology and Critical Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, National General Hospital of Dr. Cipto Mangunkusumo, Indonesia. Jln. Diponegoro No. 70. Jakarta, Indonesia.
Phone: 085643606817; Email: herikurniawan.md@gmail.com

How to cite this article :

CYTOMEGALOVIRUS CO-INFECTION COMPLICATING SEVERE PNEUMONIA IN A CRITICALLY ILL ELDERLY PATIENT WITHOUT CLASSICAL IMMUNOSUPPRESSION

INTRODUCTION

Pneumonia remains a leading cause of death globally and a major contributor to hospitalizations, with a substantial proportion of patients requiring intensive care and mechanical ventilation each year.[1,2] Despite advances in management, mortality among patients with severe pneumonia admitted to the intensive care unit remains high.[2,3] While bacterial pathogens are the most common etiologies, co-infections with viral pathogens, including cytomegalovirus (CMV), are increasingly recognized in critically ill populations without classical immunosuppression.[4,5] The global population is aging rapidly, accompanied by a growing burden of multimorbidity and increased vulnerability to critical illness.[6,7] Aging is associated with progressive alterations in immune function, known as immunosenescence, which results in impaired cellular immunity, reduced viral control, and increased susceptibility to severe infections.[7–9] Consequently, older adults may exhibit a state of functional immunocompromise, even in the absence of classical immunosuppressive conditions such as human immunodeficiency virus infection or organ transplantation.[10–12]

CMV infection is a well-recognized cause of severe disease in immunocompromised hosts. However, its clinical relevance in non-classically immunocompromised critically ill patients is increasingly recognized but remains incompletely understood.[4,13] Reactivation of latent CMV has been reported in intensive care settings and may be associated with adverse clinical outcomes.[5,17–21]

Despite increasing recognition, CMV infection in non-classically immunocompromised critically ill patients remains underdiagnosed, and its clinical significance continues to be debated.[5,15,16] In particular, its role in non-resolving pneumonia and prolonged respiratory failure remains unclear, and distinguishing CMV as a bystander from a clinically significant pathogen remains a key diagnostic challenge.[22–24] Given these uncertainties, clinically detailed reports are needed to better understand the impact of CMV reactivation on disease course and therapeutic decision-making in this population. We report a case of an elderly patient with multiple comorbidities who developed severe pneumonia requiring intensive care support, with confirmed CMV co-infection potentially contributing to a prolonged and complicated clinical course. This case highlights the importance of considering CMV in non-resolving pneumonia, particularly in the context of prolonged ventilator dependency.

CASE PRESENTATION

An 82-year-old female with multiple comorbidities, including chronic kidney disease on maintenance hemodialysis, heart failure with preserved ejection fraction, atrial fibrillation, and type 2 diabetes mellitus, was admitted due to decreased level of consciousness. For approximately one week prior to admission, the patient had been increasingly somnolent, responding only briefly to questions and quickly returning to sleep after stimulation. There was no history of fever.

The patient was referred to our team due to copious sputum that was difficult to expectorate. She had previously received inhalation therapy. On initial examination, oxygen saturation (SpO_2) was 97% with supplemental oxygen via nasal cannula at 4 L/min, and bilateral coarse crackles were noted on lung auscultation. Treatment was subsequently adjusted to include increased frequency of nebulization, mucolytic therapy, empiric antibiotics, regular suctioning, and chest physiotherapy. Sputum culture was also planned.

During hospitalization, the patient's respiratory condition progressively worsened, as evidenced by increased work of breathing and escalating oxygen requirements, eventually requiring a non-rebreathing mask at 13 L/min, with an oxygen saturation of 98% and a

respiratory rate of 24 breaths per minute. Clinically, the patient developed delirium with moderate to severe work of breathing. Given the clinical deterioration, the patient was transferred to the intensive care unit.

In the ICU, the patient exhibited further decline in consciousness, responding only to painful stimuli. Oxygen therapy was escalated from a non-rebreathing mask to high-flow nasal cannula (HFNC) with a flow of 60 L/min and FiO_2 of 50%. Hemodynamic status remained stable without the need for vasopressor support.

On hospital day 4, bronchoscopy was performed due to retained secretions and suspected airway obstruction. Bronchoscopic findings revealed tracheobronchial mucosal inflammation with abundant mucopurulent secretions, without evidence of endobronchial obstruction. Bronchoalveolar lavage (BAL) samples were obtained for microbiological evaluation, including bacterial and fungal cultures as well as molecular testing; however, no microbial growth was identified.

A pneumonia panel from sputum revealed multiple gram-negative organisms, including *Klebsiella pneumoniae* (10^6 copies/mL), *Pseudomonas aeruginosa* (10^5 copies/mL), and *Acinetobacter calcoaceticus–baumannii complex* (10^4 copies/mL), as well as *Streptococcus agalactiae* (10^4 copies/mL).

Despite escalation to targeted broad-spectrum antimicrobial therapy, including ceftazidime–avibactam in combination with aztreonam, the patient showed no significant clinical improvement, with persistent respiratory failure and difficulty in ventilator weaning. Given the discrepancy between adequate antimicrobial coverage and persistent clinical deterioration, further evaluation for alternative etiologies, including opportunistic infections and viral reactivation, was pursued.

Polymerase chain reaction (PCR) testing for cytomegalovirus (CMV) from blood specimens was positive, with a viral load of 4.75×10^3 IU/mL, consistent with CMV reactivation, raising suspicion of its contributory role in the ongoing pulmonary process.

The patient was subsequently treated with intravenous ganciclovir, in combination with ongoing antibacterial therapy. Following the initiation of antiviral therapy, the patient demonstrated gradual clinical improvement, as evidenced by improved oxygenation and stabilization of respiratory status, allowing continued progression in ventilator weaning.

Radiological findings were consistent with the clinical course. Initial chest radiography demonstrated bilateral pulmonary infiltrates, with persistent and evolving opacities observed on serial imaging. After initiation of antiviral therapy, subsequent chest radiographs showed gradual improvement in pulmonary opacities, in line with the observed clinical recovery (Figure 1).

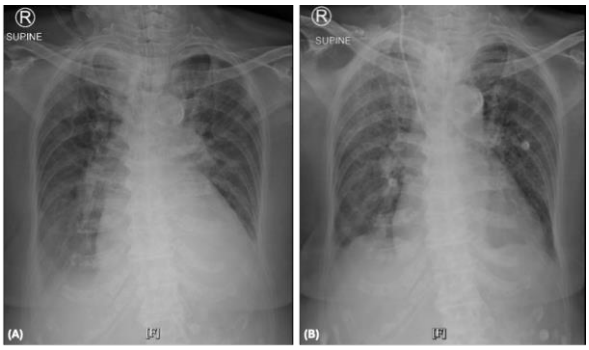

Figure 1. Serial chest radiographs in an elderly patient with severe pneumonia. (A) Initial chest radiograph showing bilateral pulmonary infiltrates. (B) Follow-up chest radiograph demonstrating improvement in pulmonary opacities after treatment.

DISCUSSION

This case highlights the complexity of managing severe pneumonia in a critically ill elderly patient, particularly in the presence of confirmed cytomegalovirus (CMV) co-infection. While CMV is classically associated with immunocompromised hosts such as transplant recipients or patients with advanced human immunodeficiency virus infection, its role in non-classically immunocompromised

populations, including elderly patients with multiple comorbidities, is increasingly recognized.[4,13,19] Importantly, the clinical relevance of CMV in this population, particularly in the setting of non-resolving pneumonia and prolonged respiratory failure, remains incompletely understood.

Aging is associated with progressive immune dysregulation, commonly referred to as immunosenescence, which results in impaired cellular immunity, reduced T-cell function, and diminished control of latent viral infections.[7–9] In this context, older adults, especially those with chronic conditions such as chronic kidney disease, diabetes mellitus, and heart failure, may exhibit a state of functional immunosuppression. This condition predisposes them not only to severe bacterial infections but also to viral reactivation, including CMV.[10,12] In critically ill patients, additional factors such as sepsis, systemic inflammation, and prolonged hospitalization may further exacerbate immune dysfunction and facilitate CMV reactivation.[14–16] These mechanisms provide a biological basis supporting CMV reactivation as a clinically relevant process rather than a mere epiphenomenon in critically ill elderly patients.

In the present case, CMV was detected in the setting of persistent respiratory failure despite appropriate antibacterial therapy. This finding, together with a measurable viral load, supports the presence of viral reactivation and suggests a potential contributory role in the ongoing pulmonary pathology. The patient also had severe bacterial pneumonia caused by NDM-producing Klebsiella pneumoniae, and the coexistence of bacterial and viral pathogens likely contributed to the severity and prolonged course of respiratory failure. Notably, the lack of clinical improvement despite targeted antibacterial therapy, followed by gradual recovery after initiation of antiviral treatment, strengthens the argument that CMV reactivation played a clinically significant role rather than representing an incidental finding. CMV has been increasingly recognized as a clinically relevant pathogen in critically ill patients, even in the absence of classical immunosuppression. Recent studies have shown that CMV reactivation in critically ill patients is associated with prolonged mechanical ventilation, increased risk of secondary infections, and higher mortality.[5,17,18,20] In this case, the patient remained difficult to wean from mechanical ventilation, further supporting the hypothesis that CMV reactivation may contribute to delayed pulmonary recovery and prolonged ventilator dependency.

The interaction between CMV and bacterial pneumonia may amplify lung injury through both direct cytopathic effects and modulation of host immune responses, leading to enhanced inflammation and impaired bacterial clearance.[19,26,27] This synergistic effect may contribute to delayed recovery, persistent respiratory dysfunction, and difficulty in ventilator weaning, as observed in this patient. Moreover, distinguishing whether CMV acts as a bystander or a true pathogenic contributor remains a clinical challenge, particularly in critically ill populations. In this context, integrating clinical course, virological data, and response to therapy is essential to support causal inference in individual cases.

Importantly, this case underscores that in patients with severe pneumonia who show suboptimal response to appropriate antibacterial therapy, clinicians should broaden the diagnostic consideration to include opportunistic infections such as CMV, particularly in cases of persistent or unexplained clinical deterioration. Clinicians should consider CMV testing in the presence of prolonged mechanical ventilation, non-resolving pneumonia despite adequate antimicrobial therapy, and persistent systemic inflammation without a clear alternative explanation.[25] Recent literature emphasizes that CMV reactivation in critically ill immunocompetent patients is often under-recognized and may contribute to worse clinical outcomes if not promptly identified.[5,15,21] Early

consideration of CMV and other opportunistic pathogens may therefore be crucial in guiding further diagnostic workup and therapeutic decisions.

From a critical care perspective, this case illustrates the challenges of managing prolonged respiratory failure in a frail elderly patient with multiple comorbidities. The presence of critical illness and underlying comorbid conditions likely contributed to difficulty in ventilator weaning, necessitating a comprehensive and multidisciplinary management approach.

Notably, although CMV reactivation has been associated with adverse outcomes, the role of routine antiviral therapy in non-classically immunocompromised critically ill patients remains controversial, and current evidence does not uniformly support its widespread use. This highlights the need for careful clinical judgment and individualized decision-making when considering antiviral treatment in this population. In the present case, the decision to initiate antiviral therapy was guided by the combination of persistent clinical deterioration, virological confirmation, and lack of response to antibacterial treatment.

Taken together, this case emphasizes the importance of considering CMV reactivation as a potential contributor to persistent pneumonia in critically ill elderly patients, even in the absence of classical immunosuppressive conditions. Beyond highlighting CMV reactivation, this report suggests that CMV may play a clinically meaningful role in prolonging respiratory failure and complicating ventilator weaning in selected patients. Early recognition of CMV in the setting of unexplained clinical deterioration may facilitate timely intervention and potentially improve clinical outcomes.

CONCLUSION

This case emphasizes that elderly patients with multimorbidity may represent a functionally immunocompromised state due to immunosenescence, placing them at risk for opportunistic infections such as CMV. In critically ill patients with severe or non-resolving pneumonia, CMV infection should be considered as a potential co-infection, particularly when the clinical course is prolonged or fails to respond to appropriate antimicrobial therapy. In particular, CMV reactivation may contribute to delayed pulmonary recovery and difficulty in ventilator weaning in selected patients. Timely recognition and appropriate evaluation of CMV may improve diagnostic accuracy and clinical outcomes in this vulnerable population. Clinicians should therefore consider CMV testing as part of the diagnostic workup in cases of persistent respiratory failure without a clear alternative explanation.

REFERENCES

1. Mattila JT, Fine MJ, Limper AH, Murray PR, Chen BB, Lin PL. Pneumonia. Treatment and diagnosis. Ann Am Thorac Soc. 2014 Aug;11 Suppl 4(Suppl 4):S189-192. doi:10.1513/AnnalsATS.201401-027PL PubMed PMID: 25148424; PubMed Central PMCID: PMC5473649.

2. Jeon ET, Lee HJ, Park TY, Jin KN, Ryu B, Lee HW, et al. Machine learning-based prediction of in-ICU mortality in pneumonia patients. Sci Rep. 2023 Jul 17;13(1):11527. doi:10.1038/s41598-023-38765-8

3. Niu J, Lv X, Gao L, Jia H, Zhao J. Development and validation of a machine learning-based prediction model for in-ICU mortality in severe pneumonia: A dual-center retrospective study. Int J Med Inf. 2025 Dec;204:106075. doi:10.1016/j.ijmedinf.2025.106075

4. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J. 2008 Mar 27;5:47. doi:10.1186/1743-422X-5-47

PubMed PMID: 18371229; PubMed Central PMCID: PMC2289809.

5. Al-Omari A, Aljamaan F, Alhazzani W, Salih S, Arabi Y. Cytomegalovirus infection in immunocompetent critically ill adults: literature review. Ann Intensive Care. 2016 Dec;6(1):110. doi:10.1186/s13613-016-0207-8 PubMed PMID: 27813024; PubMed Central PMCID: PMC5095093.

6. United Nations Department of Economic and Social Affairs. World Population Ageing 2020: Highlights: Living Arrangements of Older Persons. Erscheinungsort nicht ermittelbar: United Nations; 2021. 1 p.

7. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol. 2017;8:1960. doi:10.3389/fimmu.2017.01960 PubMed PMID: 29375577; PubMed Central PMCID: PMC5767595.

8. Müller L, Di Benedetto S. Immunosenescence and inflammaging: Mechanisms and modulation through diet and lifestyle. Front Immunol. 2025 Dec 4;16:1708280. doi:10.3389/fimmu.2025.1708280

9. Nikolich-Žugich J. Author Correction: The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol. 2018 Oct;19(10):1146–1146. doi:10.1038/s41590-018-0205-0

10. Pawelec G. Age and immunity: What is "immunosenescence"? Exp Gerontol. 2018 May;105:4–9. doi:10.1016/j.exger.2017.10.024 PubMed PMID: 29111233.

11. Pangrazzi L, Meryk A. Molecular and Cellular Mechanisms of Immunosenescence: Modulation Through Interventions and Lifestyle Changes. Biology. 2024 Dec 27;14(1):17. doi:10.3390/biology14010017

12. Onder T, Alkan S, Dogan E, Sener A. CMV reactivation in immunocompetent critically ill intensive care unit patients: a retrospective study. J Infect Dev Ctries. 2024 Oct 31;18(10):1583–9. doi:10.3855/jidc.19430 PubMed PMID: 39616489.

13. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol. 2021 Dec;19(12):759–73. doi:10.1038/s41579-021-00582-z PubMed PMID: 34168328; PubMed Central PMCID: PMC8223196.

14. Walton AH, Muenzer JT, Rasche D, Boomer JS, Sato B, Brownstein BH, et al. Reactivation of multiple viruses in patients with sepsis. PloS One. 2014;9(2):e98819. doi:10.1371/journal.pone.0098819 PubMed PMID: 24919177; PubMed Central PMCID: PMC4053360.

15. De Brabander J, Ong DSY, Cremer OL, Bos LDJ, Peters-Sengers H, Van Der Poll T. Cytomegalovirus reactivation and the host immune response in patients with sepsis. J Infect. 2025 Dec;91(6):106657. doi:10.1016/j.jinf.2025.106657

16. Morris AC, Smielewska A. Viral infections in critical care: a narrative review. Anaesthesia. 2023 May;78(5):626–35. doi:10.1111/anae.15946 PubMed PMID: 36633460; PubMed Central PMCID: PMC10952373.

17. Lachance P, Chen J, Featherstone R, Sligl WI. Association Between Cytomegalovirus

Reactivation and Clinical Outcomes in Immunocompetent Critically Ill Patients: A Systematic Review and Meta-Analysis. Open Forum Infect Dis. 2017;4(2):ofx029. doi:10.1093/ofid/ofx029 PubMed PMID: 29497626; PubMed Central PMCID: PMC5781329.

18. Luyt CE, Combes A, Nieszkowska A, Trouillet JL, Chastre J. Viral infections in the ICU. Curr Opin Crit Care. 2008 Oct;14(5):605–8. doi:10.1097/MCC.0b013e32830f1e12 PubMed PMID: 18787457.

19. Imlay H, Limaye AP. Current Understanding of Cytomegalovirus Reactivation in Critical Illness. J Infect Dis. 2020 Mar 5;221(Supplement_1):S94–102. doi:10.1093/infdis/jiz638

20. Faleiros De Azevedo FKS, Carmo Sousa EC, Brandini Néspoli JH. Cytomegalovirus reactivation in critically ill or immunocompromised patients increases mortality. Int J Fam Community Med. 2025;9(3):85–90. doi:10.15406/ijfcm.2025.09.00386

21. Schildermans J, De Vlieger G. Cytomegalovirus: A Troll in the ICU? Overview of the Literature and Perspectives for the Future. Front Med. 2020;7:188. doi:10.3389/fmed.2020.00188 PubMed PMID: 32500076; PubMed Central PMCID: PMC7243473.

22. Marcantonio ER. Delirium in Hospitalized Older Adults. Solomon CG, editor. N Engl J Med. 2017 Oct 12;377(15):1456–66. doi:10.1056/NEJMcp1605501

23. Al Farsi RS, Al Alawi AM, Al Huraizi AR, Al-Saadi T, Al-Hamadani N, Al Zeedy K, et al. Delirium in Medically Hospitalized Patients: Prevalence, Recognition and Risk Factors: A Prospective Cohort Study. J Clin Med. 2023 Jun 7;12(12):3897. doi:10.3390/jcm12123897 PubMed PMID: 37373591; PubMed Central PMCID: PMC10299512.

24. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. The Lancet. 2014 Mar;383(9920):911–22. doi:10.1016/S0140-6736(13)60688-1

25. Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. Crit Care. 2009;13(3):R68. doi:10.1186/cc7875 PubMed PMID: 19442306; PubMed Central PMCID: PMC2717427.

26. Cimendag HC, Sayiner A, Gokmen AN, Avkan-Oguz V. Risk Factors for Cytomegalovirus Reactivation and Its Impact on Clinical Outcomes in Immunocompetent Seropositive Patients Admitted to the Intensive Care Unit: A Single-Center Prospective Observational Study. Infect Dis Clin Microbiol. 2025 Jun 26;7(2):174–84. doi:10.36519/idcm.2025.480

27. Kim JY, Lee CM, Ahn YH, Lee HY, Lee SM, Jo HJ, et al. Cytomegalovirus reactivation in the lower respiratory tract as an independent risk factor for mortality in critically Ill patients. Crit Care. 2025 May 2;29(1):177. doi:10.1186/s13054-025-05324-8