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Case Series

Clinical Characteristics and Imaging Findings of Adult COVID-19 and Influenza-related Pulmonary Complications due to Methicillin-susceptible *Staphylococcus aureus*

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Abstract **Background**: The pulmonary characteristics of *Staphylococcus aureus* (*S. aureus*) co-infection with respiratory viruses, such as SARS-CoV-2 and influenza virus, are still unclear. **Case series**: Two patients with methicillin-susceptible *S. aureus* (MSSA) infection in the lungs co-infected with either SARS-CoV-2 or influenza virus are reported. Case 1 was a 66-year-old woman who was admitted with SARS-CoV-2 infection. Her chest X-ray and computed tomography (CT) showed multiple cavity formations with infiltration shadows, and MSSA was detected from her sputum and blood, suggesting COVID-19-related bacterial pneumonia and pulmonary embolism. No catheters had been used, but she had skin eruptions and a history of SARS-CoV-2 vaccination. Ampicillin/sulbactam (ABPC/SBT) was administered, and she finally improved. Case 2 was an 87-year-old man with a history of atopic dermatitis who was admitted with moderate pneumonia, and influenza virus co-infection was found. He showed multiple cavitary shadows, and MSSA was isolated from both his sputum and blood. He was diagnosed with influenza-related bacterial pulmonary embolism. No catheters had been used, but he had a history of influenza vaccination. He was also treated by ABPC/SBT and finally improved. **Conclusions:** These cases suggest that MSSA showed affinity to the lungs when co-infected with either SARS-CoV-2 or influenza virus, and it presented as septic emboli without catheter use. We should consider MSSA infection when patients have SARS-CoV-2 or influenza virus co-infection, and multiple cavity formation and skin disorders are seen, even though they were vaccinated and no catheters were used.

Keywords: COVID-19, Influenza, Bloodstream Infection, *Staphylococcus aureus*, Vaccine

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1. Background

SARS-CoV-2 and influenza virus are representative respiratory viruses, and secondary bacterial pneumonia is well known as one of the important complications [1, 2]. However, the rate of secondary pneumonia in COVID-19 was suggested to be from 3% to 15% [3, 4]; it was considered that pure viral pneumonia was predominant, although in influenza infection, secondary bacterial pneumonia was common, and more than 30% of influenza pneumonia patients were found to be co-infected with bacteria [5]. The excessive use of antibiotics and the appearance of resistant bacteria have been concerns previously based on the philosophy of antimicrobial stewardship, but we might have to use antibiotics for patients with the omicron subvariant of SARS-CoV-2, especially in the BA.5 era, in the same manner as for influenza because secondary bacterial pneumonia has been suggested to increase in elderly persons infected with SARS-CoV-2 [6].

Among the pathogenic bacteria of pneumonia, *Staphylococcus aureus* (*S. aureus*) is one of the representative pathogens, and the number of patients infected with it when the patients are co-infected with influenza suggests the affinity of influenza virus [7,8]. In addition, *S. aureus* is well known as a pathogen of bloodstream infections related to catheter use, frequently showing multiple nodular lesions rather than infiltration shadows in the lungs, suggesting septic embolization [9].

In this report, two cases of septic embolization to the lungs, one in a COVID-19 patient and one in an influenza co-infected patient, without catheter use are presented. Although the affinity between SARS-CoV-2 and *S. aureus* remains unclear, it has been suggested that SARS-CoV-2 might have affinity to *S. aureus* similar to that of the influenza virus.

These cases and the related study were approved as #2022-032 by the Institutional Review Board of Saitama Medical University International Medical Center on July 06, 2022 and registered as UMIN000047691, and #2021-2-154 by the Institutional Review Board of Tohoku Medical and Pharmaceutical University Hospital on March 15, 2022. The patients whose specimens were used provided written, informed consent to have their case details and any accompanying images published.

2. Case Series

2.1. Case 1

A 66-year-old woman with chronic renal failure was admitted to our hospital because she developed a cough and fever on day -1. She had received no vaccinations for SARS-CoV-2, but she had a 10-year history of chronic renal failure and atopic dermatitis.

SARS-CoV-2 antigen (Ag) in the nasal swab showed a mild titer, 501 IU (Cobas SARS-CoV-2 Ag, Roche, Basel, Switzerland). Infiltration shadows and nodules were found on chest X-ray and computed tomography (CT) on day 0 in her right lung field (Figure 1A, B), and arterial oxygen saturation (SpO_2) was 95% (O_2 2-L mask). She was diagnosed with severe COVID-19 pneumonia.

Laboratory data on admission at our university hospital were as follows: white blood cell (WBC) count, 7.66 x 10^3/μL, with 81.7% neutrophils, 11.2% lymphocytes, 7.0% monocytes, 0.0% eosinophils, and 0.1% basophils; platelet count, 18.7 × 10^4/μL; hemoglobin, 13.3 g/dL; blood urea nitrogen, 36.5 g/L; serum creatinine, 1.22 mg/dL; aspartate aminotransferase (AST), 46 U/L; alanine aminotransferase (ALT), 27 U/L; and C-reactive protein (CRP), 22.782 mg/dL.

Antiviral therapy with remdesivir (Gilead, Foster City, CA, USA) drip infusion 200 mg, followed by 100 mg per day for 5 days and dexamethasone 6 mg intravenously, was started.

Her pneumonia remained stable, but it was not improved on day 3. Chest X-ray and CT findings also worsened. There were widespread infiltration shadows and multiple nodules with cavity formation (Figure 1C, D). Methicillin-susceptible *Staphylococcus aureus* (MSSA) was isolated on blood culture. No venous catheters had been used. Therefore, it was suspected that the MSSA might enter from the peripheral drip infusion and/or skin lesions of atopic dermatitis including decubitus ulcer. Antibiotic therapy (ampicillin/sulbactam (ABPC/SBT) 3 g twice/day) was started, and her condition finally improved.

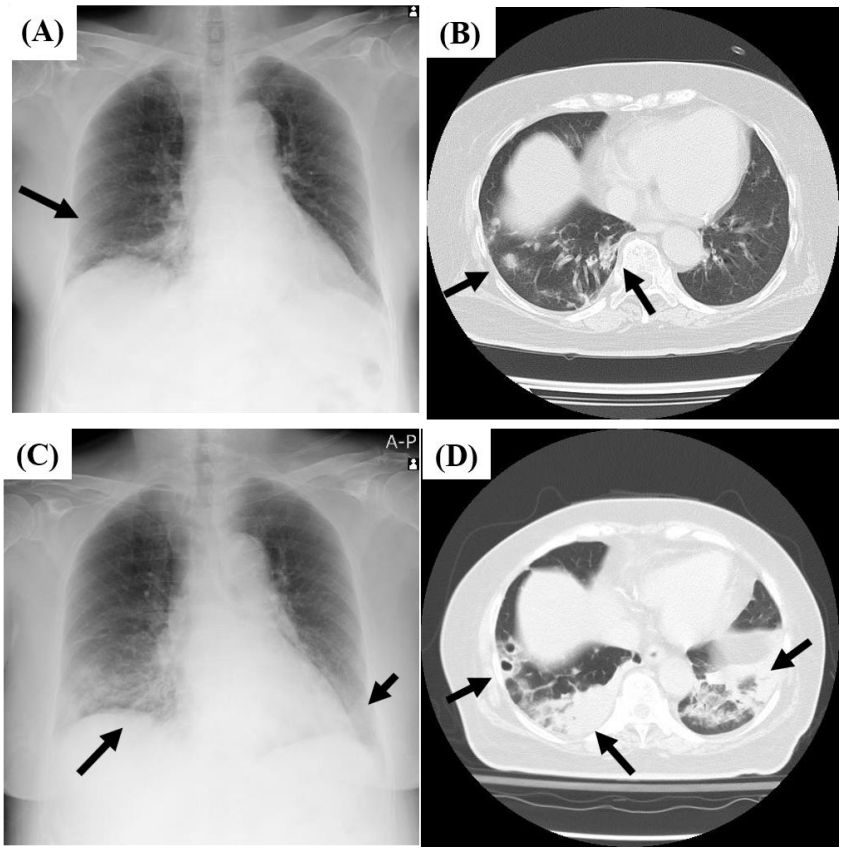

Figure 1. Chest X-ray (A) and CT (B) of the case 1 patient on admission. Infiltration shadows and nodules are seen on chest X-ray and computed tomography (CT) on day 0 in her right lung field (Figure 1A,B), but these lesions are widespread, and there are multiple nodules with cavity formation on day 3 (Figure 1C,D).

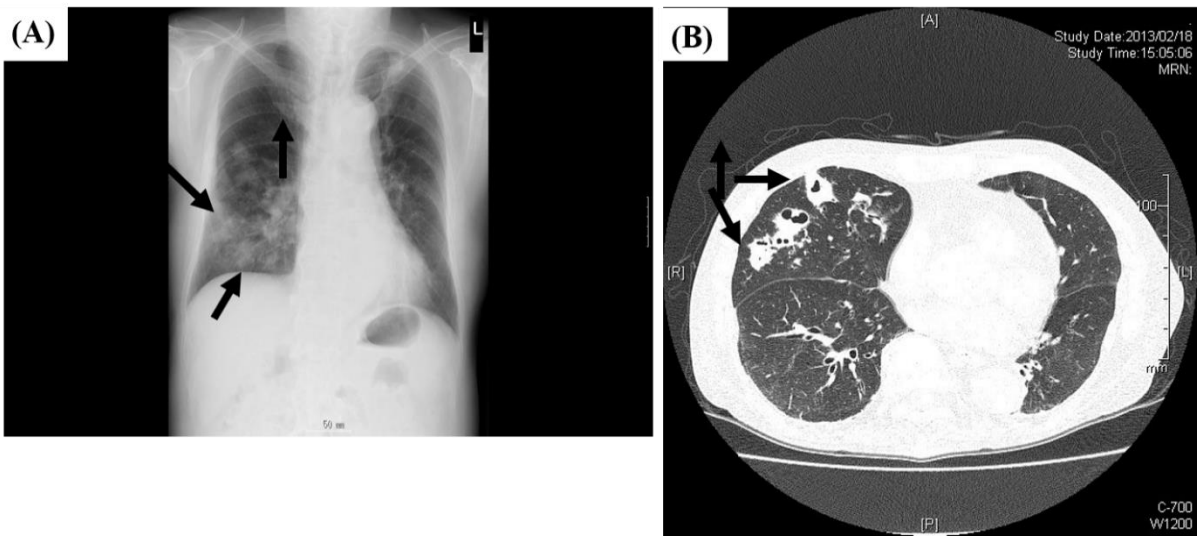

Figure 2. Chest X-ray (A) and CT (B) of the case 2 patient on admission. Peripheral nodular shadows with cavities in the right lung field are found based on the slight ground-glass opacity lesions (Figure 2A,B)

2.2. Case 2

An 83-year-old man with renal cancer and a history of atopic dermatitis had been admitted to our hospital, and he developed a fever and general malaise on day 1. The

antigen test for SARS-CoV-2 (Cobas SARS-CoV-2 Ag) was negative, but the influenza rapid antigen test (Espline A&B, Fujirebio, Tokyo, Japan) became positive. He had a past history of vaccination for influenza in that season.

Laboratory data on admission to our hospital were as follows: WBC count, 12.10 x 10^3/μL, with 86.7% neutrophils, 17.7% lymphocytes, 10.1% monocytes, 0.7% eosinophils, and 0.3% basophils; platelet count, 49.8 × 10^3/μL; hemoglobin, 11.9 g/dL; blood urea nitrogen, 14.4 g/L; serum creatinine, 1.37 mg/dL; estimated glomerular filtration rate (eGFR) 30.1 mL/min/1.73 m^2; AST, 31 U/L; ALT, 26 U/L; and CRP, 21.343 mg/dL. Chest X-ray and CT showed peripheral nodular shadows with cavities in the right lung field (Figure 2A, B), and SpO_2 was 94% by nasal canula at 2 L.

Peramivir 300 mg intravenously was given once, and sulbactam/ampicillin 3 g twice per day was given intravenously due to suspected bacterial pneumonia, especially *S. aureus, Streptococcus pneumoniae,* and aspiration pneumonia, based on the chest X-ray findings.

Two days later, MSSA was isolated from his blood and sputum, and the diagnosis was influenza-related septic embolization caused by MSSA. It was suspected that the MSSA might enter from the peripheral drip infusion and/or skin lesions of atopic dermatitis including decubitus ulcer. His fever decreased (<37 °C), and SpO_2 also improved to 96% on room air.

3. Discussion

Viral infection contributes to bacterial spread by providing more adhesion sites, causing cell and tissue structural alteration, and impairing the immune system response. The increased morbidity and mortality associated with bacterial pneumonia acquired following viral infections, including influenza infection, are well appreciated [8, 10, 11].

S. aureus, a gram-positive coccus, may complicate influenza infection that increases *S. aureus* adherence to host pharyngeal cells [8]. This phenomenon increases patients' mortality within two to seven days from bacterial coinfection. Available evidence does not allow an accurate estimate of the prevalence of bacterial coinfection with COVID-19.

However, in the present cases, *S. aureus* might also have contributed to causing severe conditions, not only in influenza, but also COVID-19, as the one of the major co-infecting pathogens, and showed similar characteristic chest X-ray/CT findings, with the presence of parenchymal consolidation and nodules with cavity formation. These phenomena suggest that *S. aureus* shows affinity with the viral infections and infection from the bloodstream, rather than respiratory infection. It has been reported that *S. aureus* infected a COVID-19 patient with breast cancer who was immunosuppressed by the administration of atezolizumab and nab-paclitaxel [12]. In that case, large areas of parenchymal consolidation and aerial bronchograms, with bilateral "ground-glass" areas reaching the highest extension in the upper and middle zones, were seen. These CT findings were similar to those of the present cases and showed the characteristics of mixed bacterial and viral infections, such as *S. aureus* and SARS-CoV-2. SARS-CoV-2 uses the angiotensin-converting enzyme 2 distributed in the human vascular endothelium as a receptor, and it thus has a strong affinity for vascular endothelial cells in particular, which facilitates vascular permeability and makes angiopathy and microthrombosis due to cytokine disease from viral infection and subsequent vascular destruction more likely than with other respiratory viruses, such as influenza [13, 14].

These are the reasons that *S. aureus*, which usually infects through the bloodstream in catheter users and skin-disrupted patients, easily co-infected patients with SARS-CoV-2. In addition, it is known that the ability of *S. aureus* to adapt to the milieu of the respiratory tract has facilitated its emergence as a respiratory pathogen in influenza patients. Its metabolic versatility, the ability to scavenge iron, coordinate gene expression, and the horizontal acquisition of useful genetic elements have all contributed to its success as a component of the respiratory flora in hospitalized patients, as a complication of

influenza, and in normal hosts [8]. These mechanisms might be a little different between those co-infected with SARS-CoV-2 and influenza virus-infected cases in the lungs of the patients, but the common reasons that *S. aureus* could co-infect influenza patients are the same as in COVID-19 patients.

Respiratory viruses are the pathogens in 38% of cases community-acquired pneumonia, but they can also be responsible for coinfections or bacterial lung superinfections [15]. The influenza virus is known to increase the susceptibility to pneumonia caused by *S. aureus*, and this latter caused 4% of cases of sepsis in hospitalized patients with cancer [16]. Furthermore, COVID-19 is a systemic disease that can affect several organs or systems (respiratory, cardiac, nervous, gastrointestinal systems, kidney, and skin) with high risk of superinfection and pulmonary embolism, requiring diverse clinical skills along with a specific radiological and laboratory workup to make the diagnosis.

4. Conclusions

Two cases of MSSA co-infection with viruses, SARS-CoV-2 and influenza virus, were presented. Both patients had been vaccinated for the infecting virus, but had skin eruptions due to atopic dermatitis. *S. aureus* might have invaded into their bloodstreams and caused characteristic pulmonary lesions, including parenchymal nodules with cavities. The preceding viral infections damaged respiratory cells, leading to the affinity to *S. aureus* as the co-infected pathogen and showed GGO in their lung fields. These patients finally improved by treatment with both antiviral agents and antibiotics, but we should consider bacterial co-infections including *S. aureus* when we see the severe and characteristic X-ray/CT findings in COVID-19 patients that are the same as in influenza patients.

COI: None

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References

[1] Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clinical Infect Dis, 2019. 68: 895-902.

[2] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis, 2020: doi: 10.1093/cid/ciaa478.

[3] Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect, 2020. 26: 1622-1629.

[4] Manohar P, Loh B, Nachimuthu R, Hua X, Welburn SC, Leptihn S. Secondary Bacterial Infections in Patients With Viral Pneumonia. Front Med (Lausanne), 2020. 5: 420.

[5] Mauad T, Hajjar LA, Callegari GD, et al. Lung pathology in fatal novel human influenza A (H1N1) infection. Am J Respir Crit Care Med, 2010. 181: 72-9.

[6] Ebina S, Seki M, Karaushi H, Shimizu A, Mitsutake K. Antibiotic prescriptions for COVID 19 patients increased during the BA.5 period. World J Med Microbiol , 2023. 2(2): 11-13.

[7] Ishida T, Seki M, Oishi K, et al. Clinical manifestations of adult patients requiring influenza-associated hospitalization: A prospective multicenter cohort study in Japan via internet surveillance. J Infect Chemother, 2021. 27: 480-485.

[8] Parker D. Impact of Type I and III Interferons on Respiratory Superinfections Due to Multidrug-Resistant Pathogens. J Infect Dis, 2017. 215: S58-S63.

[9] Ye R, Zhao L, Wang C, Wu X, Yan H. Clinical characteristics of septic pulmonary embolism in adults: a systematic review. Respir Med, 2014. 108: 1-8.
[10] Seki M, Yanagihara K, Higashiyama Y, et al. Immunokinetics in severe pneumonia due to influenza virus and bacteria coinfection in mice. Eur Respir J, 2004. 24: 143-149.
[11] Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med, 2019. 200: e45-e67.
[12] Spoto S, Valeriani E, Riva E, et al. A Staphylococcus aureus Coinfection on a COVID-19 Pneumonia in a Breast Cancer Patient. Int J Gen Med, 2020. 30: 729-733.
[13] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet, 2020. 395: 1417-8.
[14] Seki M. Trends in the management of infectious disease under SARS-CoV-2 era: From pathophysiological comparison of COVID-19 and influenza. World J Virol, 2021. 10: 62-68.
[15] Ieven M, Coenen S, Loens K, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. Clin Microbiol Infect, 2018. 24: 1158-1163.
[16] Torres VB, Azevedo LC, Silva UV, et al. Sepsis-associated outcomes in critically Ill patients with malignancies. Ann Am Thorac Soc, 2015. 12: 1185-1192.