

# A Rare Fatal Case of COVID-19 Co-Infection with Community-Acquired Methicillin-Resistant *Staphylococcus Aureus* in a Diabetic Patient

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**Background:** The co-infection of COVID-19 with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is rare but can lead to severe outcomes, especially in diabetic patients with impaired immune function. CA-MRSA, especially PVL-positive strains, can exacerbate COVID-19 symptoms and drive rapid disease progression.

**Patient and Methods:** We present a case of a 53-year-old diabetic female patient with poor glycemic control, who was hospitalized with COVID-19 and rapidly progressed to severe pneumonia. Despite antiviral treatment with Paxlovid and dexamethasone, as well as antimicrobial therapy with piperacillin-tazobactam, her condition deteriorated, leading to respiratory failure requiring extracorporeal membrane oxygenation. A post-mortem sputum culture confirmed MRSA on the day following the patient's death.

**Conclusion:** This case underscores the critical need for screening and treating bacterial co-infections in COVID-19 management, particularly in immunocompromised hosts, due to the enhanced pathogenicity of CA-MRSA strains. Early recognition and appropriate antimicrobial therapy are essential in reducing the impact of such co-infections.

**Keywords:** COVID-19, methicillin-resistant *Staphylococcus aureus*, co-infection, diabetes mellitus, pneumonia

## Introduction

The global spread of COVID-19 has escalated the incidence of pulmonary co-infections.<sup>1</sup> Notably among bacterial co-infections, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) stands out due to its resistance to conventional antimicrobial agents. The virulence of CA-MRSA, particularly strains carrying the Pantón-Valentine leukocidin (PVL) gene, can significantly exacerbate COVID-19 symptoms and contribute to rapid disease progression.<sup>2</sup> Patients with diabetes are at higher risk for infections, including MRSA, attributed to their impaired immune function and propensity for poor wound healing.<sup>3</sup> The co-infection of COVID-19 with CA-MRSA in diabetic patients is infrequently reported and can lead to severe clinical outcomes due to the synergistic effects on the immune system. We report the case of a diabetic female patient in China who was co-infected with COVID-19 and CA-MRSA, resulting in death.

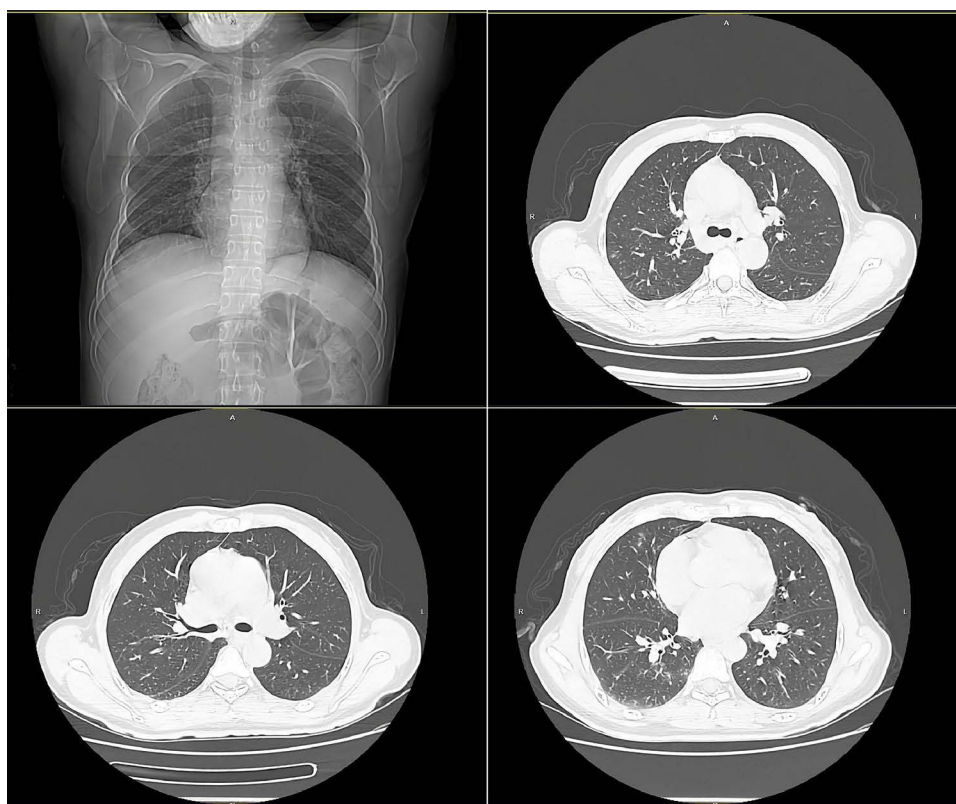
## Case Report

On Sep 17, 2023, a 53-year-old female patient presented to the infectious disease department at Alaer Hospital with a 3-day history of fever up to 40.3°C, chills, myalgia, and a 1-day history of productive cough with hemoptysis and chest pain. Upon symptom onset, she was treated with oseltamivir and ibuprofen at a local clinic, but without symptomatic relief. The patient with underlying type 2 diabetes mellitus presented with poor glycemic control despite concurrent treatment with insulin and oral hypoglycemic agents. The patient had no previous COVID-19 infections or vaccinations.

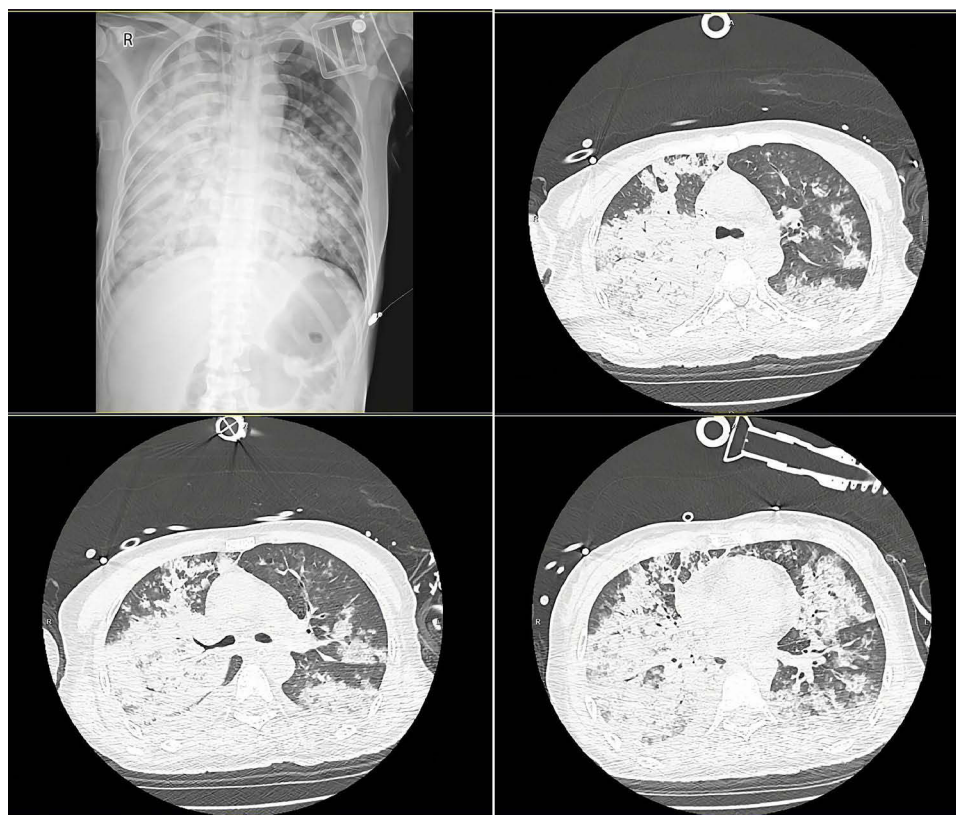
On admission, a physical examination showed coarse breath sounds without rales. Peripheral leukocyte count was  $3.75 \times 10^9$  cells/L (86.3% neutrophils, 9.9% lymphocyte, 3.7% monocytes), platelet count was  $93 \times 10^9$ /L and C-reactive

protein (CRP) level was 5.3 mg/L. Glycemic assessment showed a random blood glucose level of 17.8 mmol/L and a glycated hemoglobin levels of 13.4%. Transaminase and creatinine level were within normal limits. A nasopharyngeal swab for COVID-19 antigen tested positive. The patient's COVID-19 nucleic acid assay was positive, with a Ct value of 27.5 for the ORF gene and 26.55 for the N gene of SARS-CoV-2 RNA. Results were negative for influenza A/B virus antigen, *Mycoplasma pneumoniae* IgM, *Chlamydia pneumoniae* IgM, cytomegalovirus IgM, and adenovirus IgM. Arterial blood gas analysis revealed a pH of 7.44, partial pressure of CO<sub>2</sub> 38.3 mmHg, partial pressure of O<sub>2</sub> 59.5 mmHg (fraction of inspired O<sub>2</sub> 21%) and lactate 0.5 mmol/L. The electrocardiogram (ECG) and cardiac auscultation were normal. Chest computed tomography (CT) scan showed findings indicative of viral infection (Figure 1).

The patient began treatment with Paxlovid (nirmatrelvir/ritonavir 300mg/100mg orally every 12 hours) and intravenous dexamethasone (5mg twice daily). On the second hospital day, her condition worsened, marked by high fever (up to 39.4°C), fatigue, increasing dyspnea, and severe chest pain. Laboratory results showed a leukocyte count  $2.51 \times 10^9$  cells/L (40.0% neutrophils, 49.6% lymphocyte, 10.0% monocytes), platelet count of  $93 \times 10^9$ /L, CRP level rising to 167.1 mg/L, and procalcitonin level of 1.19 ng/mL. Cardiac enzyme panel, troponin, and N-terminal pro b-type natriuretic peptide were all within normal limits. Owing to clinical progression and suspicion of secondary bacterial infection, the patient was given piperacillin-tazobactam, a  $\beta$ -lactam antibiotic, in addition to the existing anti-COVID-19 treatment. Repeat arterial blood gas analysis revealed a pH of 6.87, partial pressure of CO<sub>2</sub> 83.8 mmHg, partial pressure of O<sub>2</sub> 80.5 mmHg (fraction of inspired O<sub>2</sub> 100%) and lactate level of 18 mmol/L. Chest CT scan demonstrated significant progression of lung infiltrates (Figure 2). The patient was diagnosed with severe pneumonia caused by COVID-19 and needed advanced life support, including intensive care unit transfer and endotracheal intubation. Despite initiating extracorporeal membrane oxygenation (ECMO) for severe respiratory failure due to COVID-19, the patient could not sustain adequate oxygenation and, sadly, died on the third hospital day (Sep 19, 2023). A sputum culture taken on admission day yielded a positive result for MRSA one day following the patient's death. The MRSA isolate, genotyped as ST338, exhibited



**Figure 1** Chest computed tomography scans of diabetic patient in China who was co-infected with COVID-19 and severe CA-MRSA pneumonia, performed on Sep 17, 2023. Images showed bilateral multifocal small patchy areas of increased density with peripheral halo signs and predominant subpleural and peribronchovascular distribution; some fibrous cord-like shadows in the right middle lobe with clear boundaries.



**Figure 2** Chest computed tomography scans of diabetic patient in China who was co-infected with COVID-19 and severe CA-MRSA pneumonia, performed on Sep 18, 2023. Images showed bilateral lungs show large consolidative opacities along the vascular bundles, predominantly in the right lung, presenting as large consolidative densities with air bronchogram signs, and the borders show mild lobular septal thickening. The trachea and bronchi are patent without significant signs of obstruction and a small amount of pericardial effusion is present. Bilateral pleural cavities show arcuate fluid densities.

resistance to antibiotics from multiple classes, including  $\beta$ -lactams (cefoxitin), tetracyclines (tetracycline), macrolides (erythromycin), and lincosamides (clindamycin), while remaining susceptible to vancomycin, gentamicin, trimethoprim-sulfamethoxazole, levofloxacin, ciprofloxacin, moxifloxacin, nitrofurantoin, rifampicin, linezolid, and tigecycline. The blood culture was unremarkable. The final diagnosis was COVID-19 co-infected with severe CA-MRSA pneumonia, resulting in the patient's death.

## Discussion

Numerous studies have concentrated on the incidence and microbial spectrum of secondary pulmonary infections among hospitalized COVID-19 patients.<sup>4,5</sup> A collective analysis of 14 observational studies reported a 16% prevalence of secondary bacterial pulmonary infections in hospitalized COVID-19 patients, ranging from 4.8% to 42.8% across studies, based on 580 cases out of 3633 patients.<sup>4</sup> *Staphylococcus aureus* was the most frequent Gram-positive bacterium causing secondary infections, responsible for 13% of cases. MRSA pneumonia, in the setting of COVID-19, typically occurred in critically ill patients needing intensive care, including mechanical ventilation, and was frequently linked to increased mortality and morbidity.<sup>6</sup> However, reports specifically addressing COVID-19 co-infections are relatively few. In a cohort of 989 patients, only 2.5% had community-acquired bacterial co-infections at COVID-19 diagnosis. Among these, patients with community-acquired co-infections, especially those with comorbidities like diabetes, were more likely to be admitted to the ICU than those without such infections.<sup>6</sup> Additionally, CA-MRSA infections were exceptionally rare in this cohort, with only two cases identified among 989 patients. The rarity of such co-infections often leads to a failure in initial empirical treatment to provide targeted antimicrobial therapies, resulting in high mortality without early diagnosis and treatment. A study published in August 2019 found the prevalence of MRSA colonization to be approximately 1.67 times higher in diabetics than in non-diabetics.<sup>7</sup> Patients with diabetes have

compromised immune function due to hyperglycemia and metabolic disorders, increasing the local MRSA bacterial load in the respiratory tract and thus raising the risk of infection.<sup>8</sup>

In this case, the patient, who had type 2 diabetes mellitus for 20 years and was on insulin and oral hypoglycemics, showed poor glycemic control, with a random blood glucose level of 17.8 mmol/L and an HbA1c of 13.4% at admission. Elevated HbA1c levels have also been identified as a significant risk factor for MRSA-induced pulmonary infections in patients with COVID-19, including those with co-infections.<sup>9</sup> Although diabetes does not seem to raise the risk of COVID-19 infection, poorly managed diabetes, lack of vaccination, and the co-infection with COVID-19 and CA-MRSA likely contributed to the rapid progression of the disease. It is well-established that diabetes can worsen COVID-19 outcomes, possibly by increasing viral tropism and cell penetration due to hyperglycemia, resulting in greater virulence and vulnerability to severe infections.<sup>10</sup> In this case, post-COVID-19 infection, the patient showed a decrease in lymphocyte counts, indicating lymphopenia. This immunosuppression, marked by lowered CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts, is typical in severe COVID-19 cases and is associated with worse clinical outcomes.<sup>11</sup> Additionally, the initial blood routine at admission showed a reduced platelet count, which is atypical for mild to moderate COVID-19.<sup>12</sup> This concurrent thrombocytopenia should alert clinicians to the possibility of an underlying bacterial co-infection or severe COVID-19.

The MRSA strain identified in this case was ST338, which harbors a smaller SCCmec V type and the PVL gene. PVL is a leukocidin that can lyse neutrophils, leading to a decrease in peripheral blood leukocyte counts. This not only impairs the innate immune response to bacterial infections but also triggers the release of reactive oxygen species and inflammatory mediators, causing further local tissue damage and contributing to necrotizing pneumonia.<sup>13</sup> In severe *Staphylococcus aureus* infections, leukopenia may result from direct cytotoxicity, immune-mediated damage, bone marrow suppression, or consumptive coagulopathy, adversely affecting immune status and prognosis. On the second day, further declines in all three blood cell lines were noted, strongly suggesting disease progression. This genotype is recognized for its heightened invasiveness, causing rapid and severe pulmonary lesions that evolved over a 24-hour period (Figures 1 and 2). Despite advanced life support measures, including ECMO and escalated antibiotics, the patient died from COVID-19 complications, exacerbated by CA-MRSA co-infection. The patient's rapid disease progression is multifactorial, underscoring the necessity of screening for CA-MRSA in community settings to facilitate early detection and treatment of infections. Given this multidrug-resistant CA-MRSA isolate's potential resistance to multiple antibiotics (including  $\beta$ -lactams, tetracyclines, macrolides, and lincosamides), treatment may require glycopeptide antibiotics or other novel antimicrobials, posing challenges for empirical clinical therapy.<sup>14</sup>

This case highlights the significant challenges in managing severe COVID-19, especially when complicated by MRSA co-infections. The unfortunate outcome underscores the necessity of screening for bacterial co-infections in COVID-19 patients to facilitate early detection and targeted treatment.<sup>15</sup>

## Abbreviations

CA-MRSA, Community-acquired methicillin-resistant *staphylococcus aureus*; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CT, Computed tomography; ECG, Electrocardiogram; ECMO, Extracorporeal membrane oxygenation; PVL, Pantón-Valentine leukocidin.

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## Ethics Statement

The study (Ethics Code: No. Lw2025001) was approved by the Ethics Review and Scientific Investigation Board of Sir Run Run Shaw Hospital, Alae Hospital, Zhejiang University School of Medicine, Alae 843300, China.



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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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