Follow the heart: A tale of possible infective endocarditis in a patient co-infected with Methicillin-resistant *Staphylococcus aureus* and Severe Acute Respiratory Syndrome Coronavirus 2

Dan-Alexandru Cozac\textsuperscript{1,2}, Ileana Voichiţa Sirbu\textsuperscript{1}, Alina Scridon\textsuperscript{2}* 

**Abstract**

**Introduction:** Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading pathogen responsible for bacteremia and valvular endocarditis. In patients with Coronavirus Disease 2019 (COVID-19), MRSA co-infection represents a challenging scenario, with increased morbidity and mortality.

**Case presentation:** We present a case of possible valvular endocarditis in a patient with acute COVID-19 and MRSA bacteremia. A 75-year-old woman presented with severe symptomatic aortic stenosis and moderate mitral stenosis. During hospitalization, she developed COVID-19 pneumonia with acute respiratory failure, and temporal and frontal intraparenchymal cerebral hemorrhage. Blood cultures were positive for MRSA, and the patient was started on a specific antibiotics regimen. The patient subsequently developed multi-organ failure and was transferred to the intensive care unit. Repeated computed tomography of the brain was consistent with a new occipitotemporal cortical hypodensity. Transthoracic echocardiography (TTE) showed a small (4 x 4 mm) mass attached to the aortic valve, but with TTE features inconclusive for infective endocarditis. The patient was scheduled for transesophageal echocardiography, but she suffered cardiac arrest, with no response to resuscitation maneuvers.

**Conclusions:** This case reveals the diagnostic and therapeutic challenges raised by MRSA and COVID-19 coinfection in a patient with preexisting valvular heart disease.

**Keywords**

aortic stenosis, methicillin-resistant *Staphylococcus aureus*, multi-organ failure, transthoracic echocardiography, valvular endocarditis

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**Introduction**

Methicillin-resistant *Staphylococcus aureus* (MRSA) valvular endocarditis requires expeditious clinical diagnosis and prompt therapeutic measures. In patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), MRSA co-infection involves an even more challenging clinical course, with rapid evolution and high mortality rates.\textsuperscript{1,2} Herein we report a case of a patient with rheumatic mitral and aortic valves stenoses, acute Coronavirus Disease 2019 (COVID-19), MRSA bacteremia, and high suspicion of valvular infective endocarditis, complicated with subarachnoid hemorrhage and ischemic stroke, multi-organ failure, and death.
Case presentation

A 75-year-old woman with a history of diabetes mellitus, percutaneous coronary intervention with drug-eluting stent implantation on the left anterior descending artery 7 months earlier, and moderate rheumatic mitral valve stenosis and severe aortic stenosis presented to the hospital with a 4-week history of typical chest pain, shortness of breath, and fatigue. The patient was a retired medical nurse, with repeated upper respiratory tract infections, and was a known MRSA nasal carrier. She was on chronic double antiplatelet, statin, beta-blocker, sartan, furosemide, and antialdosterone therapy. She was on metformin for glycemic control and had no recent intranasal treatment for MRSA. On physical examination, she was afebrile, and had a blood pressure of 100/56 mmHg, a heart rate of 55 bpm, a respiratory rate of 16 breaths/min, and oxygen saturation of 94% in ambient air. A grade 5/6 systolic murmur was audible at the right upper sternal border, with radiation to the carotid arteries. She had signs of peripheral edema and rheumatoid nodules at her fingers’ joints. The rest of the examination was normal.

Laboratory tests revealed mild normocytic anemia, serum creatinine of 1.45 mg/dL (estimated glomerular filtration rate [eGFR] of 38 mL/min/1.73 m²), and a potassium level of 5.5 mmol/L. The rest of the routine biochemical values were in the normal range. Surface electrocardiogram showed sinus rhythm with a ventricular rate of 55 bpm and signs of left ventricular hypertrophy (Figure 1). Transthoracic echocardiography (TTE) showed a left ventricular ejection fraction of 55%, with normal ventricular dimensions, severe mitral annular calcification, thickened mitral leaflets, with restriction of the posterior leaflet (Figure 2A), and moderate mitral stenosis (mitral valve area 1.4 cm² by pressure half-time; Figure 2B). The TTE also revealed gross aortic valve calcification and an aortic gradient of 103/65 mmHg (Figure 2C). No definite vegetation was identified. Coronary angiography revealed minimal in-stent restenosis and a 50-75% right coronary artery stenosis, with negative fractional flow reserve. Carotid ultrasonography was negative for significant atherosclerosis.

The initial clinical evolution was characterized by acute worsening of renal function (creatinine 1.72 mg/dL; eGFR 30 mL/min/1.73 m²), interpreted in the context of contrast agent administration. Intravenous
hydration was initiated, and spironolactone and sartan therapies were discontinued. Soon after, renal function improved (creatinine dropped to 1.50 mg/dL and eGFR increased to 36 mL/min/1.73 m²). On the 8th day of hospitalization, the patient developed chills, dry cough, and hoarseness. Given the epidemiologic context (the COVID-19 pandemic), a real-time polymerase chain reaction test for SARS-COV-2 was performed, which confirmed COVID-19 infection. At that time, lungs were clear at auscultation, without crackles or signs of respiratory failure. Two days later, the patient developed a fever (39°C), and a computed tomography (CT) scan of the lungs was consistent with left lower lobe consolidation (Figure 3). A routine blood test revealed neutrophilia (8,530/µL), high C-reactive protein levels (2.47 mg/dL) and erythrocyte sedimentation rate (60 mm/h), and signs of acute kidney injury (creatinine 1.8 mg/dL; eGFR 29 mL/min/1.73 m²). Three sets of blood cultures were initially performed. While waiting for the results, an infectious disease specialist recommended broad-spectrum antibiotics (meropenem), together with specific antiviral medication for COVID-19 (remdesivir).

Despite hemodynamic stability, the patient became somnolent and aphasic. Shortly after, oxygen saturation dropped to 85%, while breathing 5 L O₂/min by nasal cannula. A CT scan of the brain was normal. Intravenous fluids, meropenem, and remdesivir were continued, and oxygen was delivered through an oxygen mask with a reservoir bag. No symptomatic improvement in neurologic status was recorded during the following days. Repeated CT scan of the brain was performed, showing temporal and frontal intraparenchymal cerebral hemorrhage, together with subarachnoid hemorrhage, without neurosurgery indications (Figure 4). By that time, all three sets of blood cultures proved to be positive for MRSA and the antibiotics regimen was adjusted according to the microbiology result (vancomycin).

The patient subsequently developed multi-organ (cardiac, respiratory, hepatic, renal) failure and coagulopathy with moderate thrombocytopenia (120,000/µL), prolonged prothrombin time (INR 1.4), and increased D-dimer (>1,600 ng/mL) and fibrinogen levels (562 mg/dL). The patient was transferred to the intensive care unit and was started on noradrenaline and dopamine for blood pressure stabilization. Two more sets of blood cultures were collected, and those were also positive for MRSA. Repeated, non-contrast CT of the brain was consistent with a new occipitotemporal cortical hypodensity, parenchymal swelling, and stationary pattern of the previously described hemorrhagic lesions (Figure 4). Shortly after, TTE evaluation showed mildly reduced left ventricular systolic function and a small (4 x 4 mm), mobile, hyperechoic mass attached to the aortic valve (Figure 6A,B), but with TTE features...
inconclusive for infective endocarditis. The patient was scheduled for transesophageal echocardiography (TEE), but her clinical condition rapidly deteriorated. Soon after, the patient suffered a cardiac arrest, with no response to resuscitation maneuvers. According to the patient's family's decision, necropsy was not performed.

**Discussions**

The present case illustrates the challenging journey of a patient with valvular heart disease who developed COVID-19 and MRSA co-infection, with high suspicion of MRSA infective endocarditis, complicated with both hemorrhagic and ischemic intracranial lesions, multi-organ failure, and death. The main particularities of this case are related to (1) the rapid evolution towards multiple systemic organ failure caused by the co-infection with SARS-COV2 and MRSA; (2) the fact that the patient's MRSA infection may have been due to reactivation of a preexisting or to a hospital-acquired pathogen; and (3) the fact that the severe cerebral vascular events may have been due to COVID-19-related coagulopathy or may have been a complication of a possible infective endocarditis.

In our patient, the MRSA infection was considered as a probable nosocomial infection. The patient was a known nasal carrier of MRSA, acquired in a community-based manner. According to her personal history, the patient had a short-term local treatment with mupirocin a few years earlier, but nasal swabs tests were not repeated. A systematic review that was performed to determine the effectiveness of different strategies for eradicating MRSA carriage demonstrated that short-term nasal application of mupirocin had a success rate of 60% at long-term follow-up. Given that this was a patient with known valvular heart disease, it would have been of particular importance to obtain a sterile nasal swab. The MRSA infection may have been acquired in the hospital or may have been the consequence of a reactivation of the preexisting pathogen as a result of the immunodepression caused by the COVID-19 infection. Both cases are seen as nosocomial infections according to the CDC criteria and none of them can be excluded in our patient.

A recent scoping review evaluated the clinical outcomes in patients coinfected with COVID-19 and MRSA, indicating sepsis as the most common complication. In that study, only 5% of patients developed multi-organ failure and this was associated with high mortality rates. Other cases of SARS-COV2-MRSA co-infection with development of respiratory insufficiency and septic state have already been reported. However, our patient had much more severe outcomes, with very rapid evolution in the setting of acute SARS-CoV-2 infection coexisting with persistent staphylococcal bacteremia, complicated with both ischemic and hemorrhagic intracerebral lesions, culminating with multi-organ failure and death. Disseminated intravascular coagulation (DIC) was also considered, given the low platelet count, elevated D-dimer level, and the

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Figure 5 - Repeated computed tomography of the brain showing new occipitotemporal cortical hypodensity and parenchymal swelling. The arrows indicate a subacute ischemic lesion in the occipitotemporal cortex together with perilesional swelling.

Figure 6 - Initial (A) transthoracic echocardiography in short axis view showing calcified aortic valves and repeated (B) echocardiography with suspicion of a small mass attached to the aortic cusp. The arrows indicate (A) a degenerative tricuspid aortic valve and (B) a small mass attached to the aortic valve.
prolongation of the prothrombin time. However, the high fibrinogen levels allowed us to exclude DIC.

The presence of fever and bacteraemia in the setting of aortic and mitral stenoses, the occurrence of cerebral ischemic lesions, and lack of DIC or other identifiable sources of embolization raised questions regarding a potential infective endocarditis. The initial work-up for suspected infective endocarditis included TTE and blood cultures, which are essential components for confirming the Duke criteria.[6,10]

In our patient, TTE showed a small, hyperechoic, mobile formation, probably attached to the non-coronary aortic cusp, but with features inconclusive for definite valvular vegetations. Doubtful TTE findings are not rare, particularly in the early stage of the disease,[11] as was the case of our patient. Moreover, approximately 15% of confirmed infective endocarditis cases have negative TTE, especially in the presence of preexisting severe degenerative valve lesions.[11] Transesophageal echocardiography is the key imaging tool for description of suspected valvular heart masses. Unfortunately, due to the severely altered clinical status and the rapid evolution to death, TEE could not be performed in our patient. Newer forms of valvular imaging, such as 18F-fluorodeoxyglucose cardiac positron-emission tomography, could be of particular interest in such cases, especially when classic imaging techniques are not feasible or inconclusive.[12,13]

In our patient, only one major (i.e., positive blood cultures) and two minor (i.e., predisposition and febrile status) criteria were fulfilled. Although intracranial hemorrhage is categorized as a minor Duke criterion, we cannot confirm with certainty that the patient’s hemorrhagic event was an endocarditis-related vascular event and not a complication of COVID-19 infection, as shown in previous studies.[14–16] The case was therefore classified as “possible” infective endocarditis. Should the suspicion of infective endocarditis have been raised earlier in this patient? One major criterion for the diagnosis of infective endocarditis is prolonged bacteremia, which was the case in our patient. However, soon after the blood cultures were positive, TTE was periodically repeated, with inconclusive results. Should we have started directly with a TEE examination? According to recent data,[17] TEE is reasonable in high-risk clinical scenarios, such as Staphylococcus bacteremia, or continued suspicion of infective endocarditis despite negative TTE, but without a clear indication due to lack of data on cost-effectiveness and excessive use of this technique. Necropsy would have been particularly relevant for establishing a definite infective endocarditis diagnosis. Unfortunately, this could not be performed in the present case.

Conclusions

The present paper describes a challenging case of possible Staphylococcus aureus valvular infective endocarditis in a patient with SARS-CoV-2 coinfection, complicated with acute intracerebral ischemic and hemorrhagic lesions, multi-organ failure, and death. This case also illustrates the limitations of transthoracic echocardiography in the diagnosis of infective endocarditis, particularly in patients with severely remodeled cardiac valves.

Conflicts of interest

none declared.