

Severe acute mitral valve regurgitation in a COVID-19-infected patient

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SUMMARY

The ongoing SARS-CoV-2 (COVID-19) pandemic has presented many difficult and unique challenges to the medical community. We describe a case of a middle-aged COVID-19-positive man who presented with pulmonary oedema and acute respiratory failure. He was initially diagnosed with acute respiratory distress syndrome. Later in the hospital course, his pulmonary oedema and respiratory failure worsened as result of severe acute mitral valve regurgitation secondary to direct valvular damage from COVID-19 infection. The patient underwent emergent surgical mitral valve replacement. Pathological evaluation of the damaged valve was confirmed to be secondary to COVID-19 infection. The histopathological findings were consistent with prior cardiopulmonary autopsy sections of patients with COVID-19 described in the literature as well as proposed theories regarding ACE2 receptor activity. This case highlights the potential of SARS-CoV-2 causing direct mitral valve damage resulting in severe mitral valve insufficiency with subsequent pulmonary oedema and respiratory failure.

BACKGROUND

This novel organism which is a single-stranded enveloped virus, SARS-CoV-2, is highly virulent, contagious and deadly with a high mortality rate in the USA.¹ This respiratory virus can also cause cardiovascular, gastrointestinal, renal, haematologic and neurological organ system dysfunction. Research shows that patients with underlying cardiovascular disease were more likely to exhibit elevated troponin T (Tn-T) levels and have more frequent complications such as acute respiratory distress syndrome (ARDS), acute coagulopathy, malignant dysrhythmias and acute kidney injury.² The pathophysiological mechanisms underlying acute myocardial injury are not well understood.³ Theories on endothelial cell infection across vascular beds may explain the broad variety of clinical manifestations of COVID-19. They include hypercoagulability, cytokine storm, stroke, myocarditis, acute renal failure and chilblains (COVID-19 toes) among others.⁴

We describe a unique case of a middle-aged COVID-19-positive man who presented with non-productive cough and progressive dyspnoea. One month into hospitalisation, the patient developed severe acute mitral valve regurgitation requiring emergent cardiac catheterisation and surgical mitral valve replacement. The postsurgical histopathological analysis of the mitral valve was consistent with COVID-19 infection. This case highlights the potential for COVID-19 infection causing valvular

damage leading to pulmonary oedema and respiratory failure secondary to congestive heart failure. In these patients, a broader differential for pulmonary oedema and respiratory failure must be considered to ensure timely and appropriate treatment.

CASE PRESENTATION

A middle-aged man presented to the emergency department with progressively worsening shortness of breath, a non-productive cough and hypoxemia. His medical history was significant for atrial flutter status post ablation in 2017. The patient is a lifelong non-smoker who bikes 2 miles daily. At that time in 2017, an echocardiogram revealed mild mitral valve regurgitation with a normal left ventricular ejection fraction (LVEF >55%). He also had a history of hypertension, asthma and chronic sinusitis. He was diagnosed with COVID-19 3 days prior to presentation to the emergency room at a local testing site. Vital signs on admission were as follows: respiratory rate of 29 breaths per minute, heart rate of 99 beats per minute, blood pressure of 132/80 mm Hg, temperature of 37.2°C and an oxygen saturation of 87% on room air. Initial physical examination revealed that the patient was in mild respiratory distress. The lung examination revealed decreased breath sounds in the right lung with scattered wheezes. On cardiac examination, no appreciable murmurs or gallops were noted. There was no lower extremity oedema.

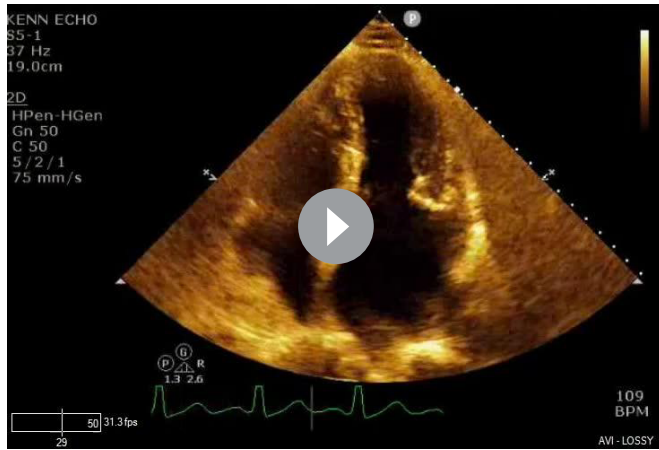
Laboratory studies on admission demonstrated a normal white blood cell count ($8.0 \times 10^3/L$), mildly elevated terminal pro B-type natriuretic peptide levels (625 pg/mL) and normal Tn-T (<0.01 ng/mL). Electrocardiography revealed sinus tachycardia with left ventricular hypertrophy. Chest radiography confirmed patchy right lower lobe opacities and peribronchial cuffing.

The patient was admitted to the medical floor, placed on 2 L of oxygen via nasal cannula and started on hydroxychloroquine, azithromycin, thiamine, vitamin C and zinc. On the second night of admission, the rapid response team was activated because of the patient's worsening respiratory condition. Arterial blood gas revealed a pH of 7.47, PaCO₂ of 23, PaO₂ of 69 and HCO₃ of 17 on 4 L nasal cannula. Over the next several days, chest radiography demonstrated increased peribronchial wall thickening, new bilateral infiltrates, bilateral pleural effusions and increased cardiac silhouette. CT angiogram of the chest ruled out a pulmonary embolism and confirmed patchy consolidative airspace disease in a bronchovascular distribution bilaterally with bilateral pleural effusions. The patient was treated with diuretics and started on



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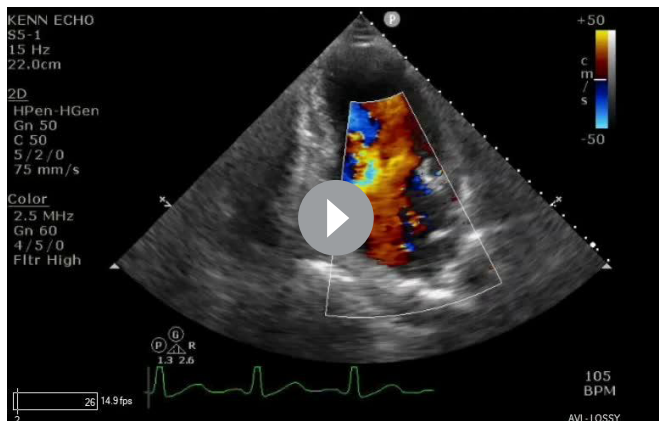


Video 1. The left ventricular systolic function is normal with an ejection fraction of 60–65%. There is severe wide-open mitral valve regurgitation due to torn chordae and flail posterior leaflet with 1.2 cm coaptation gap measured.

methylprednisolone 80 mg every 8 hours. On the fourth night of admission, the patient was found to be in rapid atrial fibrillation. Chest radiography confirmed progression of bilateral infiltrates. He was placed on 15 L high flow oxygen and transferred to the intensive care unit. Over the next several days, he was started on anticoagulation for suspicion of pulmonary microthrombi, received convalescent plasma and was maintained on diuretics. Eventually, his oxygenation improved, he was transferred back to the medical floor and over the next few weeks his oxygen requirements decreased to 4 L nasal cannula.

One month into his hospitalisation, the patient reported acute onset dizziness, intermittent chest pain and developed acute hypotension. His electrocardiogram confirmed atrial fibrillation. Tn-T levels remained <0.01. An echocardiogram was performed showing a normal LVEF of 60%–65%, wide-open mitral valve regurgitation with torn chordae and a flail posterior leaflet (video 1). There was severe, wide-open/torrential mitral regurgitation (video 2). CXR revealed worsening bilateral pulmonary oedema. The left atrium was noted to be enlarged both on chest imaging and echocardiogram (figure 1).

The patient was transferred to the coronary care unit for further haemodynamic evaluation and stabilisation. An intra-aortic balloon pump was placed due to preoperative cardiogenic shock. He underwent both left and right heart catheterisation which confirmed severe mitral valve regurgitation with a pulmonary



Video 2. There is severe, wide -open torrential mitral regurgitation.

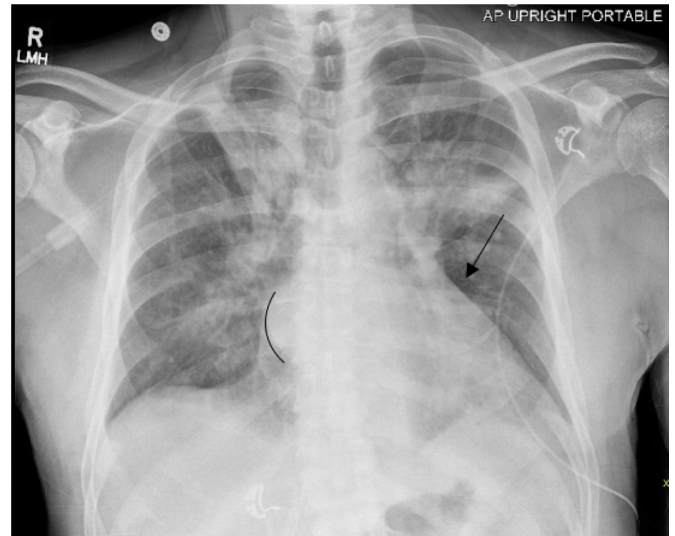


Figure 1 Chest radiography demonstrates left atrial enlargement with a double density sign (arc) and a straight left heart border (arrow). Cardiomegaly present.

artery capillary wedge pressure of 52 mm Hg, minimal coronary disease with only 40% stenosis of the proximal right coronary artery and moderate pulmonary hypertension with a pulmonary artery pressure of 42 mm Hg. Intraoperatively, he was found to have wide-open mitral regurgitation, with a flail posterior leaflet and torn chordae, along with annular calcifications. Subsequently,

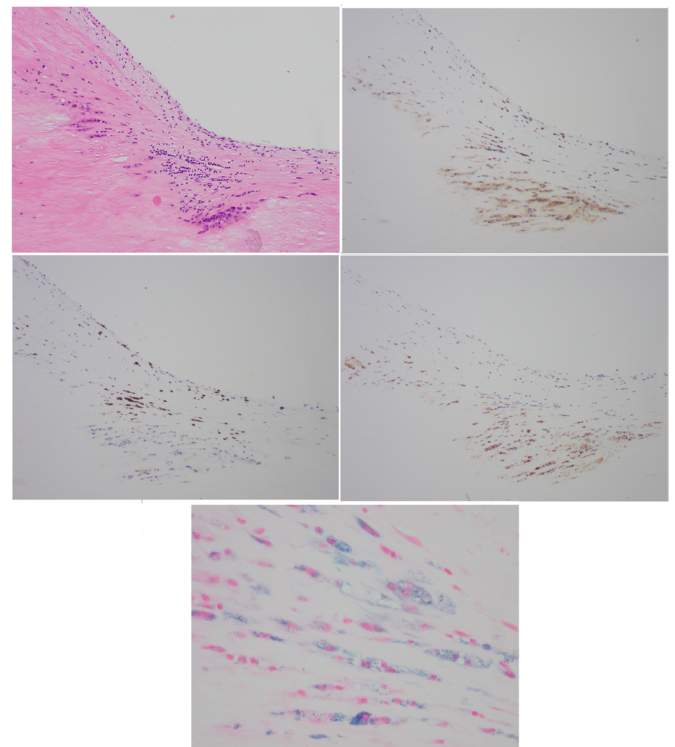


Figure 2 Tissue sections reveal valvular tissue with patchy chronic lymphohistiocytic inflammation (H&E-stained section, top left). A CD3 immunostain highlights the T-cell predominant infiltrate (top right) that is composed exclusively of a CD4 T helper subset (middle left). CD68 highlights tissue macrophages (middle right). A special stain for iron demonstrates haemosiderin deposition largely within macrophages (bottom middle).

the patient underwent surgical mitral valve replacement with a biosynthetic prosthesis and a left atrial appendage exclusion with an atrial clip was placed.

Histopathological evaluation of the valve revealed myxomatous degeneration. There was an inflammatory infiltrate composed of T lymphocytes and histiocytes. Immunohistochemistry identified these T cells as the CD4 helper subtype. There were no CD8+ T cells. Of note, there was no significant acute inflammation or neutrophils, which are commonly seen in acute bacterial endocarditis. A CD68 immunostain highlighted numerous tissue macrophages. Iron stain highlighted haemosiderin deposition within these macrophages. These findings suggest a subacute to chronic nature of the inflammatory process (figure 2). Valve and blood cultures were negative for bacterial, viral and acid-fast bacilli. The 16s ribosomal RNA test was negative. Three days postoperatively, the patient was extubated and weaned off vasopressors. He developed a postpericardiotomy acute pericarditis with Mobitz type I second degree AV block. He was treated with colchicine. An electrophysiologic evaluation determined a permanent pacemaker was not indicated. He was discharged home in stable condition.

OUTCOME AND FOLLOW-UP

A few weeks after discharge from the hospital, the patient returned with a DVT in his left lower extremity. He is now being treated with warfarin. He continues to follow-up with pulmonary and cardiology outpatient. The patient has returned back to work and his strength has improved greatly.

DISCUSSION

As the pandemic continues, anecdotes of cardiovascular organ dysfunction in patients with COVID-19 increases steadily. The pathophysiological mechanisms underlying acute myocardial injury in COVID-19 are not well understood.³ Theories on endothelial cell infection across vascular beds may explain the broad variety of clinical manifestations of COVID-19. They include hypercoagulability, cytokine storm, stroke, myocarditis, acute renal failure and chilblains (COVID-19 toes) among others.⁴

Common cardiac manifestations of COVID-19 infection include myocarditis, cardiac arrest, myocardial infarction and dysrhythmias.⁵ Patients with underlying cardiovascular disease are more likely to have elevated Tn-T levels which can lead to ARDS, acute coagulopathy and malignant dysrhythmias.² Interestingly, our patient's Tn-T levels remained <0.01 throughout his hospitalisation, suggesting that ischaemic cardiac injury was not a confounding factor. Although our patient did have a history of atrial flutter status post ablation 3 years earlier, his echocardiogram at that time demonstrated mild mitral valve regurgitation with a normal LVEF (LVEF >55%). He was physically active and biked several miles a day and therefore ischaemic cardiomyopathy was not suspected. The patient's lack of prior symptoms, such as chest pain or dyspnoea, since his prior echocardiogram in 2017 suggests no or minimal progression of his mild mitral regurgitation over time. Furthermore, cardiac catheterisation revealed minimal coronary artery disease. This patient was treated with hydroxychloroquine and azithromycin during his hospitalisation. These medications can cause prolongation of the QT interval leading to ventricular dysrhythmias. To date there is no evidence that these medications cause valvular heart disease. The patient's only dysrhythmia was atrial fibrillation. Acute mitral valve regurgitation may have a variable presentation depending on the severity of the valvular insufficiency and the integrity of the subvalvular apparatus. The patient was

asymptomatic prior to hospitalisation and no audible murmur was heard on physical examination, therefore we believe his mitral valve was intact and more durable prior to COVID-19. However, the murmur can be subtle due to rapid equalisation of left atrial and left ventricular pressure gradients, and up to 50% of patients may have no audible murmur.⁶ The initial working diagnosis was ARDS. However, due to the patient's declining condition, with worsening respiratory failure and increasing infiltrates on chest imaging studies, a cardiac aetiology was considered. Pulmonary oedema secondary to ARDS can initially be challenging to differentiate from a cardiogenic cause as demonstrated in this case. Although bilateral pulmonary oedema is often noted with cardiogenic etiologies, a unilateral presentation has been described in the literature with an occurrence of 2%.⁷⁻⁹ Clinical suspicion and prompt imaging with echocardiography can establish the diagnosis and guide the appropriate intervention in a timelier fashion.¹⁰

Several proposed mechanisms of COVID-19-related cardiac involvement include: ACE2 receptor-mediated myocardial injury, cytokine storm mediated by an imbalanced response and dysregulation among subtypes of T helper cells and hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis.^{11 12} ACE2 has been identified as the receptor for SAR-CoV-2, mediating its entry into host cells.¹³ There have been reports of ACE2 receptors in myocardial tissue, thus, leading to myocardial pathology.¹⁴ Additionally, ACE2 has been detected on cardiac valves, especially aortic valves in humans, thus leading to aortic valve stenosis. Research has shown that possible downregulation of the ACE2/angiotensin (107)/Mas receptor axis may promote fibrosis and inflammation in cardiac valves, thus causing valvular sclerosis and insufficiency.¹⁵

In spite of these proposed mechanisms of COVID-19-related cardiac involvement, there are very little data on the exact immune cells involved in this process, likely due to the inability to obtain tissue samples during the pandemic. In a recent paper done by Fox *et al*, relevant pulmonary findings in COVID-19-positive autopsy reports revealed mild-to-moderate lymphocytic infiltrates composed of CD4+ and CD8+ lymphocytes. CD4+ lymphocytes could be seen in aggregates around small vessels, some of which appeared to contain platelets and small thrombi.¹⁶ Furthermore, histological sections of cardiac autopsies revealed that lymphocytes were adjacent to surrounding degenerating myocytes, which may represent an early manifestation of viral myocarditis.¹⁶ Chen *et al* hypothesised that pericytes that have high levels of ACE-2 receptors are targets for viral-induced cardiac injury and may result in capillary endothelial cell dysfunction, including microvascular dysfunction.¹⁷ We propose that if capillary endothelial cell dysfunction occurs adjacent or surrounding the valvular apparatus, acute valvular insufficiency is a possible mechanism of viral injury. The inflammatory cells seen on our patient's pathological examination of the mitral valve are similar to the lymphocytic infiltrates seen in prior cardiopulmonary autopsy sections of patients with COVID-19.¹⁷

Tavazzi *et al* proposed that myocardial injury could be caused by direct injury to the myocytes as a result of migration of infected macrophages from the lung, as seen in a case report of a COVID-19-infected patient who developed acute cardiac injury seen on endomyocardial biopsy.¹⁸ This is another possible mechanism that could have led to the immune cells seen in our mitral valvular tissue. Atreya *et al* describes a case report of myocardial infarction resulting in chordae rupture and severe mitral regurgitation. Although their patient tested negative for COVID-19 through a reverse transcription PCR assay, it is very likely that

Patient's perspective

Beginning to explain this journey is difficult and confusing. I was planning to travel to my home town to sit out what I thought might be the balance of the pandemic shut down. I thought it would be responsible of me to get tested. The process was very well organised. Vehicles were directed along the spiral of a parking deck, completing forms as you go. Once completing the instructed swabbing, drivers were asked to pull over into designated parking spots to wait for their results. After not more than 10 min I got a call on my cell telling me that I was 'positive' and that I needed to wait in place for someone to bring instructions to my vehicle. It took not more than another 10 min for a person to approach me. I was given a packet of instructions repeating the care worker's words to go home, stay home and call 9-1-1 if I felt any advancement of symptoms.

I felt fine—no symptoms. Or so I thought. I have been an asthmatic all my life and as an adult I would have infrequent but familiar occurrences of wheezing and shortness of breath. Such had been happening for at least 4 or maybe even 6 weeks prior to any public conversation about COVID-19. It was not so much wheezing as it was shortness of breath along with dry coughing—sometimes rather severe and always only as I settled into bed. I had gotten comfortable—sufficiently enough to eventually get to sleep—with a formula of cough medicines and teas and organic supplements. Along with this ritual for 3–4 nights a week, I stepped up my weekly workout routine as well. The timing of these nightly symptoms clearly predated any intuitive connection to the virus. And as I started working out more, I was feeling better at night.

But now I had been told I was infected with this virus. The very next evening after testing, I realised I had not slept and that I was not sleepy. Another day passed and still no sleep, nor was I sleepy. But now I also realised I had not eaten and felt no urge at all to want to eat. The third night I focused on sleep with meditation. I fell asleep only to be awakened by that same hard dry hacking cough and shortness of breath. The shortness of breath was stunning enough that I got dressed and called 9-1-1.

I was always the well-informed-always-watching-the-news grandfather talking to everybody about being safe and smart. I was the guy giving encouragement to friends when we all heard that a young peer had contracted the virus and died shockingly fast just a couple of weeks before. I was the guy giving encouragement to my family as we learnt that a young dear cousin had succumbed to being on a ventilator fighting this virus. I am that guy with the habit of years before keeping sanitiser on each door panel of my vehicle. A can of Lysol in the passenger-side door panel, and using them almost every time I reentered my vehicle. I was that guy still heeding my mother's constant nudging during my childhood to 'not touch things as much as possible'. And most of my adult life, I was that strange guy who pushed open doors with a closed fist or my elbow. By old habit, I try to never touch a door knob. I probably touched the railing of a stairway or an escalator or a moving sidewalk in an airport, only a handful of times and only out of purposeful curiosity. I had endured three sinus surgeries and kept hospital face masks in my car, using them frequently. Yet I was looking around and trying to explain to my family through spontaneous texting, 'How did I end up in a COVID room?'

I was beginning to see firsthand that medicine is indeed a 'practice'. All I wanted to do was cooperate with them. Make their challenge as easy as I possibly could. Give back to them as

Continued

Patient's perspective Continued

much sensitivity and compassion as I could, limited there, as I was. If only others could see these people as I was seeing them. Could feel their spirit, their fears even, their determination, amid so much death and the isolated chance to learn how to keep someone else alive.

Eyes: I may never be able to adequately explain what you start to see in eyes when all you see are eyes. Every single conceivable emotion and experience and story can be felt and told through a human's eyes. This is especially the case when you study the regimented process they all followed as they enter your room with full hazmat suiting, and how they methodically removed all hazmat covering in the same receptacle at the door before leaving my space. These were all regular people just like me. So many varied ethnicities with family concerns like me. With fears like me. With curiosities like me. With dreams like me. Careful and cautious like me. With social challenges like me. Some were just at work and others carried the weight of work, just like me. Some just wanted to go home safe and others were on a mission. Some were fascinated by the learning of it all and others seemed to be walking by nothing more than determination to defeat despair. The deeper translation 'I see you,' becomes the definitive of every human interaction.

My perspective as a patient and survivor feels empty without reflection on the people—specific people—the concert of personalities and the ballet of body languages. My recovery was something managed by people. The science that kept me alive was administered and managed by individual people. People at the hands of God and universal energy, saved my life. They are still studying how to save my life.

I still have the blood clot. I understand it is a slow and careful process. About once each week, I feel a numbness and lack of control in that leg, which goes away slowly after about 5 min or 10 min. I feel a slight numbness in my hands every now and then. Nerves in my left hand are damaged (maybe not permanently) and I cannot clasp things tightly. I understand that to be the result of so many needles. I experience a rather severe and slowly developing pain that feels like a muscle spasm, which starts under my right shoulder blade and travels around to the front of my rib cage. It never lasts more than 5 min or 10 min. Sometimes it comes in my hips and pelvis. And sometimes I feel a little weakness or even dizziness requiring me to be still or rest a bit. But my heartbeat is healthy and strong. Overall, I have gotten stronger. I have gained back most of my weight. I said goodbye to oxygen tanks, and I am walking the treadmill and doing other exercises for rehab conditioning. And oddly, my sinus problem seems to have disappeared—so far.

More importantly, now every morning, even this Wednesday morning as I write, feels like a Sunday morning. A new sun. A new week. Full of reverence. Not without purpose and work to do. But easy.

there was inflammation that contributed to the ruptured papillary muscle.¹⁹ We believe that the flail posterior leaflet and torn chordae that was seen in our patient was caused by the damage of the massive cytokine storm and immune cells, similarly which are seen in prior COVID-19-positive autopsy reports and the inflammation seen on prior mitral valve chordae apparatus.^{16 19} Furthermore, our patient's 16s ribosomal RNA test was negative and blood cultures remained negative, which definitively ruled out bacterial aetiology. In an interesting case report done by

Learning points

- ▶ Acute mitral regurgitation may radiographically resemble acute respiratory distress syndrome, therefore the differential diagnosis of respiratory failure in COVID-19 infections should include acute mitral valve insufficiency.
- ▶ Radiographic findings of left atrial enlargement should prompt clinicians to suspect underlying valvular abnormalities.
- ▶ Clinical suspicion of underlying cardiac dysfunction and prompt imaging with echocardiography can establish the diagnosis and guide the appropriate intervention in a timely fashion.
- ▶ Survivors of COVID-19, especially those with prior or acquired heart disease, should be examined for cardiac dysfunction periodically after recovery.

Bernal-Torres *et al*, they described a young female with no prior cardiac history developing fulminant myocarditis secondary to COVID-19, confirmed via the inflammatory process seen on cardiac MRI. Although they were not able to obtain an endomyocardial biopsy, this case report highlights that fulminant myocarditis is a potential complication that occurs in COVID-19-infected patients, regardless of their prior cardiac history.²⁰

Although there are many causes of viral myocarditis, such as adenovirus, enterovirus and parvovirus B-19, there are very few cases of viruses causing damage to specifically the cardiac valves. Since the beginning of the pandemic, there have been a number of cases of viral myocarditis, but few to none which involved the cardiac valves. Given the data from prior autopsy reports, along with the case reports seen in COVID-19-induced myocarditis, we conclude that our patient's acute mitral valve regurgitation was secondary to COVID-19-induced myocardial injury.

In the ever-changing landscape of the novel COVID-19 pandemic, we want to bring attention to a unique and emergent case of respiratory failure secondary to acute mitral valve regurgitation. This case highlights that COVID-19 infection can cause direct damage to the mitral valve leading to valvular insufficiency and subsequent cardiogenic pulmonary oedema and respiratory failure. The pathological specimen from this case demonstrates lymphocyte-induced mitral valve damage leading to severe insufficiency and resultant congestive heart failure. Acute mitral regurgitation may radiographically resemble ARDS and may also occur simultaneously as in our case. Therefore, the differential diagnosis of respiratory failure in COVID-19 infections should include acute mitral valve insufficiency.

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