Pulmonary Fibrosis vs. ARDS in the Setting of Amiodarone during Treatment for Complications of COVID-19 Pneumonia

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Introduction

The first cases of Coronavirus Disease-2019 (COVID-19) hit the United States in late December 2019 and COVID-19 reached pandemic status by March 2020. Currently, person-to-person spread is known to be via airborne and droplet transmission.[1] After a mean incubation period of around 5 days, nonspecific symptoms may manifest, the most common being fever, dry cough, and dyspnea. In fatal COVID-19 cases, progression of symptoms leads to acute respiratory distress syndrome (ARDS), requiring mechanical ventilation, and ultimately, multiple organ failure. There is currently no definitive treatment for COVID-19, although vaccines and supportive care, such as maintaining vital signs and addressing complications, have been implemented.[2] One year later, the virus continues to surge and new demographics of the infected have changed from mostly the elderly to middle-aged people with comorbidities such as diabetes, obesity, respiratory diseases, and the immunocompromised. We present a case of ARDS vs. pulmonary fibrosis in the setting of amiodarone use that developed during the COVID-19 pandemic, specifically during the flare of the omicron variant, in Elmira, NY.

Case Presentation

On November 21, 2021, a 53-year-old man presented to the Arnot Ogden Medical Center Emergency Department with worsening symptoms of cough, shortness of breath, dizziness, nausea, fatigue, and poor oral intake after testing positive for COVID-19 three days prior at an urgent care. Significant past medical history included type 2 diabetes mellitus, atrial fibrillation status post cardioversion, hypertension, and obesity. He was unvaccinated against COVID-19 at the time of admission. He was a former smoker with a 12 pack year history. Home medications included metformin HCL 500 mg PO BID, Lisinopril 2.5 mg PO daily, and OTC ibuprofen PRN. Upon initial presentation, he had an oxygen saturation on room air of 63%. He was immediately placed on high flow nasal cannula, which corrected his oxygen saturation to 92%. His temperature was 97.2°F, heart rate 101 beats per minute, respiratory rate 24 breaths per minute, and blood pressure 138/69 mmHg. On auscultation, bilateral coarse breath sounds with wheezing were heard in all lung fields. Chest CT demonstrated moderate-to-severe patchy interstitial opacities predominantly in the bilateral mid to lower lungs and extensive bilateral ground-glass infiltrates consistent with COVID-19 pneumonia; chest X-ray showed mixed consolidative and ground glass air space opacities (Figure 1). His EKG showed sinus rhythm with premature atrial complexes in a pattern of bigeminy and a heart rate of 81 bpm; there were no axis deviations or ST elevations or depressions noted. A COVID-19 PCR test resulted positive. His labs at presentation showed hyponatremia, elevated inflammatory markers, and lactic acidosis (Table 1). The patient was admitted to the ICU and treated according to COVID-19 treatment protocols.

On hospital day 2, the patient developed acute onset retrosternal chest pain overnight. 12-lead ECG showed ST elevations in leads II, III, aVF, and V3-V6, as well as ST depressions in leads I and aVL. Along with findings of elevated troponin >11,000 and ongoing cardiac symptoms, cardiology was consulted and the patient was urgently transported to the cath lab, which revealed complete occlusion of the posterior descending artery and partial occlusion of the lateral circumflex artery. Echocardiogram done the next morning found a slightly reduced ejection fraction of 50-55% with evidence of wall motion abnormalities with hypokinesis of basolateral, inferolateral, and inferior myocardium. The patient was continued on heparin drip for 48 hours followed by therapeutic Lovenox. Home medications of aspirin, Plavix, lisinopril, and atorvastatin were resumed. Post procedure, the patient developed atrial fibrillation with rapid ventricular response, controlled with beta-blockers. IV amiodarone was initiated with improved rate control. The patient was later transitioned to oral amiodarone 200 mg PO daily.

The patient was in ICU for more than a month on high flow oxygen making nominal improvement and at times worsening oxygen saturation levels. Repeat chest x-ray done on hospital day 32 showed worsening pulmonary status taking on the appearance radiographically and clinically or ARDS. This prompted the discontinuation of amiodarone due to concerns of medication-induced pulmonary fibrosis. Use of incentive spirometry and continued care resulted in slow improvement with eventual weaning from BiPAP to vapotherm to nasal cannula oxygen. After nearly 3 months in the hospital, oxygen requirements had decreased to 6-8 liters at rest with oxygen saturation of 90%. Follow-up WBC, CRP, and ESR showed no indications of active inflammation.

Laboratory test	Result on admission	Reference range
WBC	8.2	4.0-11.0 10x3/uL
Hgb	15.8	13.2-17.1 g/dL
Hct	44.5	38.5-50.0%
Plt	334	150-450 10x3/uL
Na	131	136-145 mmol/L
K	3.9	3.5-5.1 mmol/L
Cl	97	98-107 mmol/L
CO2	19	21-31 mmol/L
Glu	250	74-109 mg/dL
BUN	29	7-25 mg/dL
Cr	1.1	0.7-1.3 mg/dL
Ca	8.7	8.6-10.3 mg/dL
Alb	3.5	4.2-5.5 g/dL
Anion gap	15	7-15 mmol/L
Mg	1.7	1.9-2.7 mg/dL
D-dimer	1150.0	0.0-230.0 ng/mL
Ferritin	>1500	24-336 ng/mL
ESR	63	0-20 mm/hr
Troponin	10	2-20 pg/mL
BNP	35	0.0-43.0 pg/mL
APTT	33.3	22.9-36.5 seconds
PT	13.6	11.0 14.6 seconds
INR	1.2	0.8-1.2
Lactic acid	2.4	0.5-1.9 mmol/L
Procalcitonin	0.92	<0.07 ng/mL

Table 1: Laboratory values on admission.

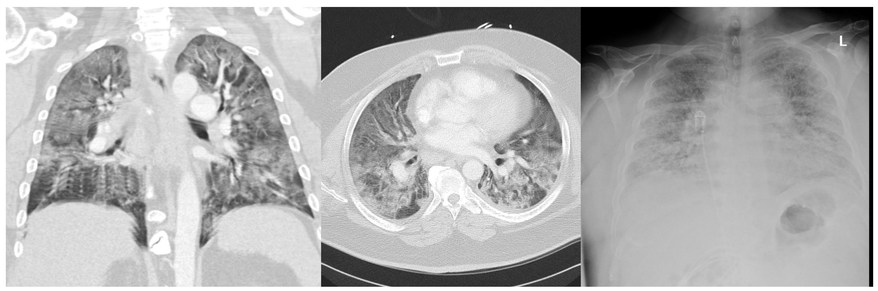

Figure 1: Coronal contrast-enhanced CT scan through the posterior mediastinum showing diffuse bilateral ground glass airspace opacification. Contrast-enhanced axial slice showing the same. Corresponding initial CXR showing diffuse consolidative and patchy air space opacities bilaterally.

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Discussion

Amiodarone is an antiarrhythmic drug used to treat both ventricular and supraventricular arrhythmias.[3] The primary mechanism as an antiarrhythmic is via blockade of voltage-gated potassium channels, which prolongs repolarization of the cardiac action potential. As a class III antiarrhythmic agent, amiodarone is a multichannel blocker of calcium, sodium, and potassium ions and a noncompetitive alpha- and beta-adrenergic blocker in cardiac cells. In addition, amiodarone has been found to possess both antioxidant and anti-inflammatory qualities via increasing activities of superoxide dismutase and levels of total glutathione, while also decreasing production of TNF-alpha and IL-6.[4,5] Furthermore, amiodarone has been found to inhibit the spread of SARS coronavirus in vitro by accumulating intracellularly and interfering with the endocytic pathway.[6] For this reason, amiodarone has been considered as a possible treatment of COVID-19 infection.[7] Given that COVID-19 appears to be associated with both the development and co-morbidity of arrhythmias, the use of amiodarone appears well-justified.[8,9] Thus, the proposed question is: can amiodarone use reduce the incidence of arrhythmias associated with COVID-19 infection and effect on the heart?

Unfortunately, the list of adverse effects of amiodarone administration is extensive, as accumulation in tissues is known to lead to issues in the thyroid (hypothyroidism, hyperthyroidism), lungs (pulmonary fibrosis, chronic interstitial pneumonitis, ARDS), liver (hepatitis, cirrhosis), CNS (peripheral neuropathy), skin (photosensitivity, blue discoloration), eyes (corneal microdeposits, optic neuritis), and heart (bradycardia, AV block).[10] Furthermore, chronic amiodarone use furthermore increases the risk of developing any of these adverse effects. COVID-19 infection itself has its own list of complications that further limit amiodarone use, including ARDS, myocarditis, CNS dysfunction (including dizziness, confusion, peripheral neuropathy), and VTE (including DVT, PE, stroke, and MI), thus giving rise to the question of the utility of amiodarone to treat arrhythmias in the setting of COVID-19 pneumonia.

The patient we describe in this case study has a past medical history of atrial fibrillation, status post cardioversion, who presented with COVID-19 pneumonia and developed STEMI and perimyocarditis. During an 83-day hospitalization, amiodarone was administered for 26 days for rate and rhythm control. Imaging shows that the patient's pulmonary picture changed from diffuse bilateral ground glass airspace opacification on 11/1 to diffuse interstitial thickening and traction bronchiectasis in a pattern consistent with fibrosis on 1/3, thus developing pulmonary fibrosis vs. ARDS in the setting of amiodarone while being treated for COVID-19 pneumonia.

Conclusion

Amiodarone is a well-known and widely used antiarrhythmic with reported use as an antioxidant and anti-inflammatory agent, as well as targeted antiviral activity against SARS coronavirus. Although this patient's cardiologic symptoms were alleviated, the patient subsequently developed pulmonary fibrosis vs. ARDS. Ultimately, he was weaned to a manageable level of oxygen supplementation that allowed for discharge. More information is needed regarding the length of administration of amiodarone and the risk of developing pulmonary symptoms, so that a proper risk-benefit analysis of amiodarone use for COVID-19 complications can be made.

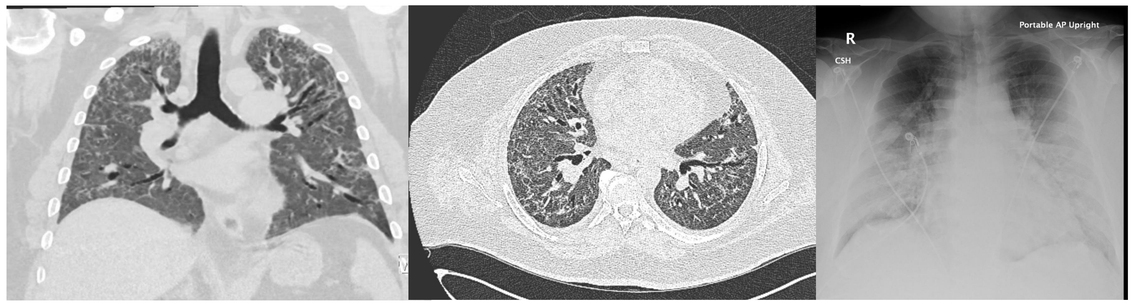

Figure 2: Unenhanced coronal CT through the level of the carina showing diffuse interstitial thickening and traction bronchiectasis in a pattern consistent with fibrosis. High resolution axial CT through the heart shows the same. Corresponding CXR shows mixed interstitial and airspace opacities.

References

1. WHO. (23 December 2021). Coronavirus disease (COVID-19): How is it transmitted? https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-how-is-it-transmitted.
2. Wu, Y., Chen, C., Chan, Y. (March 2020). The outbreak of COVID-19: An overview. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7153464/.
3. Heijman, J., Dobrev, D. (April 2013). Pleiotropic actions of amiodarone: still puzzling after half a century. https://pubmed.ncbi.nlm.nih.gov/23568552/.
4. Polat, B., Cadirci, E., Halici, Z., Bayir, Y., Unal, D., Bilgin, B., Yuksel, T., Vancelik, S. (July 2013). The protective effect of amiodarone in lung tissue of cecal ligation and puncture-induced septic rats: a perspective from inflammatory cytokine release and oxidative stress. https://pubmed.ncbi.nlm.nih.gov/23579385/.
5. Matsumori, A., Ono, K., Nishio, R., Nose, Y., Sasayama, S. (September 1997). Amiodarone inhibits production of tumor necrosis factor-alpha by human mononuclear cells: a possible mechanism for its effect in heart failure. https://pubmed.ncbi.nlm.nih.gov/9315521/.
6. Stadler, K., Ha, H., Ciminale, V., Spirli, C., Saletti, G., Schiavon, M., Bruttomesso, D., Bigler, L., Follath, F., Pettenazzo, A., Baritussio, A. (August 2008). Amiodarone alters late endosomes and inhibits SARS coronavirus infection at a post-endosomal level. https://pubmed.ncbi.nlm.nih.gov/18314540/.
7. Aimo, A., Baritussio, A., Emdin, M., Tascini, C. (October 2021). Amiodarone as a possible therapy for coronavirus infection. https://pubmed.ncbi.nlm.nih.gov/32295404/.
8. Carpenter, A., Chambers, O., Harchi, A., Bond, R., Hanington, O., Harmer, S., Hancox, J., James, A. (May 2020). COVID-19 Management and Arrhythmia: Risks and Challenges for Clinicians Treating Patients Affected by SARS-CoV-2. https://pubmed.ncbi.nlm.nih.gov/32432127/.
9. Kochav, S., Coromilas, E., Nalbandian, A., Ranard, L., Gupta, A., Chung, M., Gopinathannair, R., Biviano, A., Garan, H., Wan, E. (June 2020). Cardiac Arrhythmias in COVID-19 Infection. https://pubmed.ncbi.nlm.nih.gov/32434385/.
10. Latini, R., Tognoni, G., Kates, R. (December 2012). Clinical Pharmacokinetics of Amiodarone. https://link.springer.com/article/10.2165%2F00003088-198409020-00002.