

CORRELATION BETWEEN PSYCHOTROPIC TREATMENT ASSOCIATED WITH QT PROLONGATION AND COVID-19-RELATED MYOCARDITIS IN A PATIENT WITH SCHIZOPHRENIA

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INTRODUCTION

Coronavirus disease 2019, or simply COVID-19 is a disease caused by novel virus named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The outbreak of COVID-19 was believed to have begun as a result of zoonotic transmission from seafood markets in Wuhan, Hubei Province in China, presenting as series of acute atypical respiratory diseases. It then expanded at an alarming rate around the world and was labeled a pandemic by WHO on March 11, 2020 (Yuki et al. 2020, Parasher 2021, Jansen van Vuren et al. 2021).

Although COVID-19 was first thought to be a purely respiratory disease, it is now known that the virus can affect other organ systems including nervous system, and lead to a broad spectrum of manifestations. One of the serious complications associated with SARS-CoV-2 is multisystem inflammatory syndrome (MIS), that can occur 2-12 weeks after initial infection. It was initially recognized in children (MIS-C), but later identified in adults (MIS-A) as well. Although the pathophysiology of both MIS-C and MIS-A is unknown, a hyperinflammatory immune response similar to that seen in Kawasaki syndrome defined as a small to medium vessel vasculitis, is hypothesized as a cause. Most common symptoms reported in MIS-A are heart-related symptoms including arrhythmias, myocarditis, pericarditis, other symptoms include abdominal pain, vomiting, diarrhea, or widespread rash (Veysseh et al. 2021, Yao et al. 2021). With the patient being at risk of cardiac involvement related to COVID-19, caution must be exercised in the management of psychiatric patients treated with drugs known to have cardiac side effects.

We report a case of a patient diagnosed with paranoid schizophrenia who died due to malignant arrhythmia, while noticeable are two distinct mechanisms of its inducement, COVID-19-related myocarditis and the treatment of his psychiatric disorder.

All procedures performed in this study were in accordance with ethical standards and the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards. Autopsy results, including histology, were used anonymously for scientific evaluation.

CASE REPORT

We present a case of a 56-year-old man diagnosed with paranoid schizophrenia F20.0 (ICD-10). His current treatment included paliperidone 9 mg/day, quetiapine 600 mg/day, zuclopenthixol decanoate 200 mg á 21 days, and sodium valproate 300 mg/day. Since 2016, he was placed in psychiatric hospital (supraregional medical facility providing comprehensive long-term psychiatric care for patients in the catchment area with approximately 850 000 inhabitants). In March 2021, he had a 10-day lasting COVID-19 infection confirmed by positive PCR test, that presented with only mild symptoms of fatigue and muscle pain. As treatment he was taking ivermectin and inosine acedoben dimepranol. At the beginning of June, he was found dead in his room. Three days prior to his death he received a first dose of vaccine Comirnaty, right before which he was tested negative on rapid antigen test. According to the available medical records he experienced no side effects after vaccination or before his death, he had no other health problems prior to his death, he died unexpectedly and suddenly.

Rapid COVID-19 antibody test performed before the autopsy showed presence of IgG and IgM antibodies in the blood, COVID-19 rapid antigen test had a negative result. Autopsy revealed mild atherosclerosis, left ventricular hypertrophy, mild cardiac fibrosis including focal papillary muscle fibrosis, severe alveolar edema, focal pneumorrhagias and brain edema. Severe diffuse interstitial myocarditis was discovered by histologic examination of myocardium of the left ventricle and papillary muscles (Figure 1).

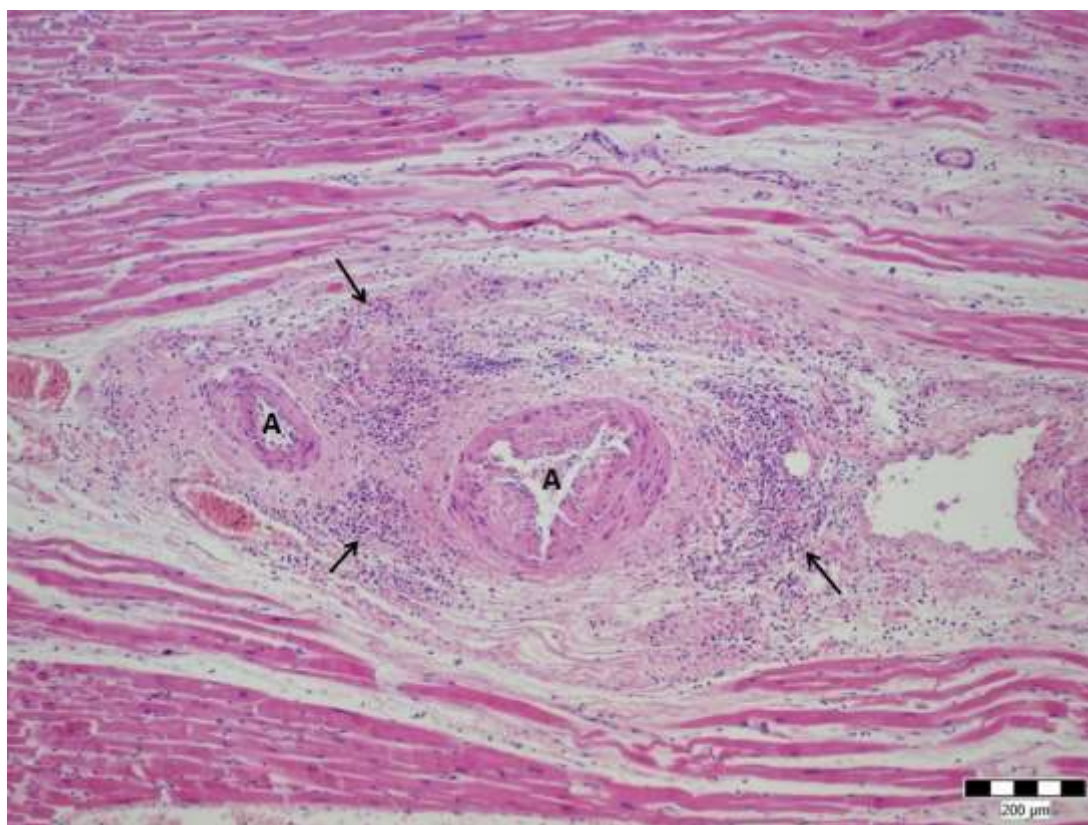


Figure 1. Lymphoplasmacytic and polymorphonuclear infiltration (arrows) surrounding small branches of coronary arteries (A) in the left ventricle (H&E, 200x magnification)

Table 1. Postmortem toxicology results

Type of sample / analytical technique	Substance	Result
Serum / GC	ethyl alcohol	negative
Urine / GC	ethyl alcohol	negative
Urine / TLC	metabolites of benzodiazepines	trace amount
	venlafaxine	positive
	quetiapine	negative
	analgetics	negative
	barbiturates	negative
	alkaloids	negative
Urine / immunoscreening	benzodiazepines	positive
Serum / LC-MS	nicotine, cotinine	positive
	venlafaxine	positive
	desmethylvenlafaxine	positive
	quetiapine	positive
	OH-quetiapine	positive
Serum / LC-MS	venlafaxine	1205.24 ng/ml
	quetiapine	1654.34 ng/ml

GS – gas chromatography; TLC – thin layer chromatography; LC-MS – liquid chromatography–mass spectrometry

Toxicology analysis of blood (Table 1) using liquid chromatography–mass spectrometry (LC-MS) showed concentration of venlafaxine was 1205,54 ng/ml and concentration of quetiapine was 1654,34 ng/ml. Determination of CYP2D6 activity proved he was a normal metabolizer.

Therapeutic dose range of quetiapine is 100-500 ng/ml, toxic dose is from 1000 ng/ml, and lethal dose is

estimated to be more than 1900 ng/ml. In case of venlafaxine, therapeutic dose range dose is 100-400 ng/ml, toxic dose is from 1000 ng/ml, and lethal dose is more than 6000 ng/ml (Schulz et al. 2012).

Death was caused by a malignant arrhythmia due to prolongation of QT interval induced by psychotropic medication in association with COVID-19-related myocarditis.

DISCUSSION

Beyond the known negative impact of COVID-19 on patients with mental disorders, long-term side effects of psychotropic medication must be considered as another problem for patients receiving concomitant COVID-19 treatment. Recent cohort studies and warnings from the European Medicines Agency and the US Food and Drug Administration Adverse Event Reporting System have been highlighting QT prolongation. As a result, the Tisdale Risk Score is being strongly recommended for assessing the risk of QT prolongation in individuals taking psychotropic medication during COVID-19 treatment. The risk score classifies patients as 'low', 'moderate', and 'high' risk based on their age, gender, prescription of loop diuretics and drugs prolonging QT interval, serum potassium concentration (≤ 3.5 mEq/L), value of QT interval at admission (≥ 450 ms), number of drugs prolonging QT interval (≥ 2), and presence of following conditions: acute myocardial infarction, sepsis, or heart failure (Nadir et al. 2021, Tisdale et al. 2013).

In our case, psychotropic drugs with a risk of QT prolongation were also administered.

Therefore, we agree with the views of the authors Crescioli et al., that when COVID-19 treatment is used together with medications that are known to increase QT intervals, caution should be exercised, as these drugs can cause conduction and repolarization abnormalities on their own. Because QT prolongation can be asymptomatic and potentially lethal, it should always be closely monitored (Crescioli et al. 2021).

CONCLUSION

The presented case, where increased concentrations of psychotropic drugs (quetiapine, paliperidone) known to prolong the QT interval may have contributed to the cardiac failure in a patient with COVID-19-related myocarditis, points out the importance of monitoring cardiovascular system (ECG at regular intervals) in psychiatric patients, particularly in relation to COVID-19. Advisable is to avoid any drug combinations that are known to prolong the QT interval. Increased caution should be exercised when it comes to COVID-19 positive patient, and patients who overcame the disease, as asymptomatic cardiac injury in MIS-A may be present. Dose of psychotropic drugs should be reduced, and their serum levels must be regularly monitored.

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Contribution of individual authors:

All authors made equal contribution to this case report in terms of drafting, writing, obtaining the patient's consent, revising the paper and approved the final version of manuscript.

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