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RESEARCH ARTICLE

Atypical Takotsubo Cardiomyopathy Secondary to COVID-19 Presenting Late as Chest Pain with Subsequent Late Sudden Death

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ABSTRACT

Background: Cardiac involvement at time of COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is associated with poor prognosis. However, post-COVID-19, the recovery period might also be associated with lingering effects or predisposition to some cardiac manifestations including sudden death, which can not only be missed but which might also remain undefined. This is a report of 56-year man who developed chest pain diagnosed as atypical Takotsubo type cardiomyopathy presenting after recovery from COVID-19 pneumonia 12 days following confirmation of SARS-CoV-2 infection by real-time quantitative polymerase chain reaction (RT-qPCR) testing.

Case Report: 56 years old male who re-presented after clinical recovery from COVID-19 pneumonia (diagnosed on 1st admission from a nasopharyngeal swab using RT-qPCR assay/test; Xpert® Xpress SARS-CoV-2 in vitro diagnostic device), with new cardiac symptoms (3rd admission), which after appropriate investigations was diagnosed as non-coronary cardiac injury/atypical Takotsubo type cardiomyopathy leading to sudden fatal outcome. Plausible mechanisms include direct cardiac toxicity (myocarditis) and/or microthrombi/hypoxia. The precise timing of the cardiac injury was difficult to elucidate but the potential for lingering cardiac consequences was realistic with eventual negative prognostic outcome.

Conclusions: This case presentation after full clinical recovery from COVID-19 pneumonia highlights the new challenges for such cases, including potential longer-term enduring impact on cardiovascular morbidity and late mortality. The implications on use/benefits from conventional cardio-protective therapies including duration remains unclear. Further studies to screen high-risk patients with elevated cardiac biomarkers or cardiac risk factors post COVID-19 recovery (if not all patients) might be helpful but at the expense of significant consequences on existing cardiac services and cardiologists.

Keywords: Coronavirus disease 2019/COVID-19, severe acute respiratory syndrome coronavirus 2/SARS-CoV-2), case report, atypical Takotsubo cardiomyopathy.

Introduction/Background

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes minimal or no symptoms with <10% cases presenting as severe/critical illness. Pre-existing morbidity suggested to increase risks for poor prognosis from COVID-19 includes obesity, organ transplantation, ongoing immunosuppression therapy, concomitant chemotherapy/radiotherapy (for any cancer) and severe chest pathologies (severe asthma/COPD and cystic fibrosis). [1]. The presumed median time from onset to clinical recovery (from respiratory and non-specific symptomology) for mild cases is approximately 2 weeks, with 3-6 weeks projected for severe/critical cases.

COVID-19 associated acute cardiac injury/involvement is projected to be between 7-20% with pre-existing cardiovascular risks (Hypertension, Diabetes Mellitus, Heart Failure, Obesity) acknowledged only as also predisposing to a 'poor prognosis/outcome'. Cardiac involvement at time of active COVID-19 infection may be identified with screening ECG and/or troponin blood levels [2, 3]. However, in patients whom have survived recent COVID lung infection, the post-COVID recovery period might also be associated with lingering predisposition to sub-clinical or overt clinical cardiac manifestations, including risks for sudden death. These risks are yet to be fully characterised, and their management also remains undefined.

Indeed, a recent study of 153,760 individuals with previous COVID-19 (along with controls) described the long-term cardiovascular outcomes of these individuals. The risk of cardiovascular disease extended well beyond the acute phase of COVID-19 and included dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease. [4]

A recent case report of typical Wellens syndrome presentation with ECG changes in an octogenarian with co-existing features of COVID-19 infection, treated medically and without undergoing coronary angiography resulted in fatal outcome within a few days [5]. The case report highlighted the importance of identifying coronary anatomy and appropriate timely intervention, irrespective of COVID-19 status as per existing international standards. In addition, as our knowledge of the mechanisms leading to cardiac presentations with coronary artery disease and/or myocardial injury in patients with active COVID-19 is improving, one key unknown is whether SARS-CoV-2 may also lead to any long-term negative cardiovascular consequences [6, 7, 8].

Takotsubo syndrome (broken heart syndrome) is characterised by left ventricular dysfunction associated with physical or emotional stress. COVID-19 is known to cause a "cytokine storm" which could provoke this syndrome [9].

This is a report of 56-year man who developed chest pain due to atypical Takotsubo type cardiomyopathy following recovery from COVID-19 pneumonia diagnosed 12 days earlier following confirmation of SARS-CoV-2 infection by real-time quantitative polymerase chain reaction (RT-qPCR) nasopharyngeal swab test.

Case Report

56-year Caucasian male, admitted in early April 2020 with respiratory COVID-19 symptoms (fever, shortness of breath with cough) with a positive COVID-19 nasopharyngeal swab test for the detection of viral RNA (SARS-CoV-2 RT-qPCR test; Xpert® Xpress SARS-CoV-2 in vitro diagnostic device; Cephid, European Union CE marked, in a UKAS accredited hospital laboratory) and radiological tests, was treated in hospital for 7-days with supportive therapy (medication, high flow nasal oxygen inhalation) and successfully discharged home (Table 1). In the absence of any specific cardiac symptoms, an ECG (electrocardiogram), troponin and BNP (Brain Naturitic Peptide) tests were not carried out during this admission. He had a significant past medical history of COPD/emphysema requiring home nebulisers, Chronic type II Respiratory Failure, previous Intravenous Drug Use (IVDU), Hepatitis C positive, previous alcohol excess, Chronic pancreatitis and Type II diabetes mellitus.

Table 1: Timeline correlating admission episodes with dates

Episode	Episode Date	Diagnosis/Test done	Discharge date
1st Admission	04/04/2020	Acute Pulmonary COVID-19 with positive swab	11/04/2020
2nd Admission	16/04/2020	New non-cardiac chest pain	16/04/2020
3rd Admission	18/04/2020	Re-presented with cardiac chest pain, and COVID-19 negative swab	
	18/04/2020	COVID-19 negative swab	
	19/04/2020	COVID-19 negative swab	
	21/04/2020	Transthoracic Echocardiogram (TTE)	
	24/04/2020	Coronary angiogram	25/04/2020

However, a few days after discharge, he was re-admitted (2nd admission) with new chest pains that were initially concluded to be non-cardiac (Figure 3: no new ECG changes, compared to previous documented ECG from a few months earlier, and Troponin negative) and he was discharged on same day. COVID-19 nasopharyngeal swab test (SARS-CoV-2 RT-qPCR) was negative on this 2nd admission.

The patient then re-presented (3rd admission) to Emergency Department (ED) 48 hours later complaining of 'on-going chest pains' - typically cardiac pain and more severe, radiating into his shoulder and left arm - and was therefore admitted for further cardiac investigations. Vital signs on admission confirmed Oxygen saturation of 93% on room air (improving to 96% on 24% nasal oxygen), Respiratory rate between 20-28/min; pulse 80/min regular, BP 142/90, Temperature 37.1◦C with normal BMI (body mass index). Chest examination confirmed bilateral minimal wheezing, Heart Sounds I and II were normal with no evidence of heart failure. With *provisional diagnosis* of another Infective Exacerbation of COPD (IECOPD) with possible unstable angina/Acute Coronary Syndrome (ACS), he was started on intravenous antibiotics (Cefotaxime), venous thromboprophylaxis (Fondaparinux) and two consecutive COVID-19 swabs were negative, with further tests (see below) requested.

Bloods tests results confirmed mild anaemia, mild neutrophilia, mild lymphopenia with thrombocytosis - (Haemoglobin 117g/dl; Normal=130-180); White cell count 9.1 (Normal=9-11.2) - Neutrophil 8.4 (Normal=1.7-7.5), Lymphocyte 0.3 (Normal=1-4.5); Platelets 610 (Normal=150-450) - and elevated C-Reactive Protein (CRP) 15.5 (Normal<6). Kidney function, including electrolytes were normal with eGFR >90. Initial and 12 hours Troponin were normal (12 and 9 respectively; Normal<20). Liver Function Test was also normal. Two repeat COVID swabs were both negative and chest X-ray/CXR (***figure 1***) showed old bilaterally reticular changes only. CT-Pulmonary Angiogram (CTPA) confirmed heart of normal size, moderate centrilobular emphysema, no effusion, no pulmonary embolism nor any persistent features of COVID-19 (***figure 2***). Compared to the old ECG done before 1st admission (***figure 3***), the 12-Lead ECG done at the time of the 3rd admission showed new T-wave inversion V2-V5 (***figure 4***), with a cardiac diagnosis of possible ACS/NSTEMI/Wellens syndrome. Following optimisation of medical therapy (Aspirin 75mg, Ticagrelor 90mg bd, Fondaparinux 2.5mg, added Ivabradine 5mg bd and ISMN SR 30mg) an urgent Cardiology review and tests were requested as he continued with anginal chest pains on treatment, and on daily activities within the ward (but responding to rest and sublingual GTN).

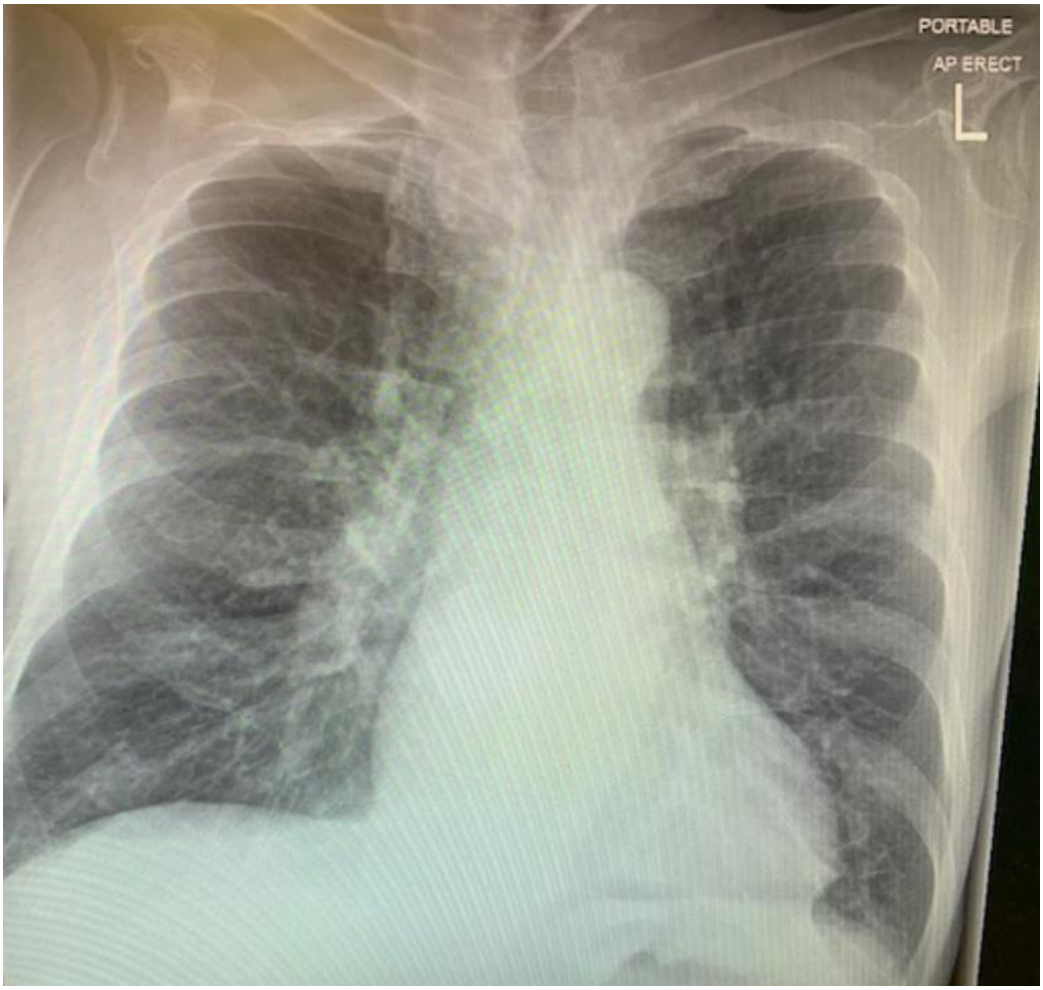

Figure 1: Chest X-ray/CXR on 3rd admission showing no features suggestive of active COVID-19 infection

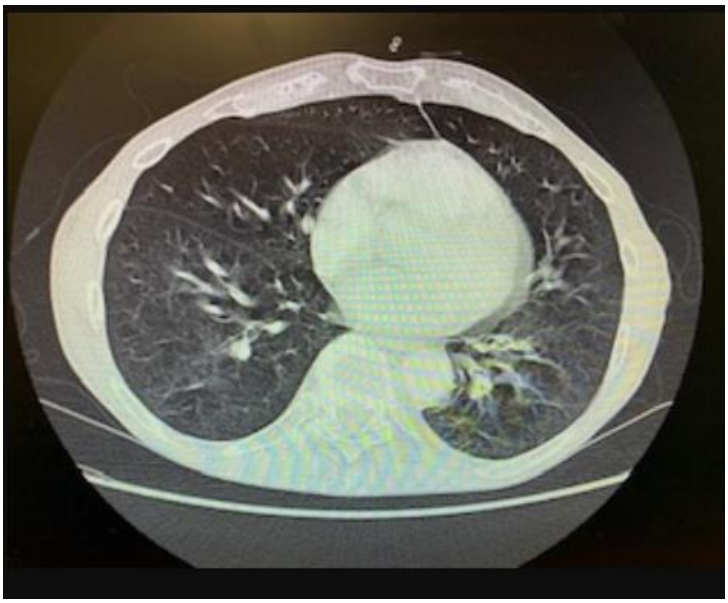

Figure 2: Computerised tomography (CT) scan of Chest on 3rd admission confirming no active features suggestive of COVID-19

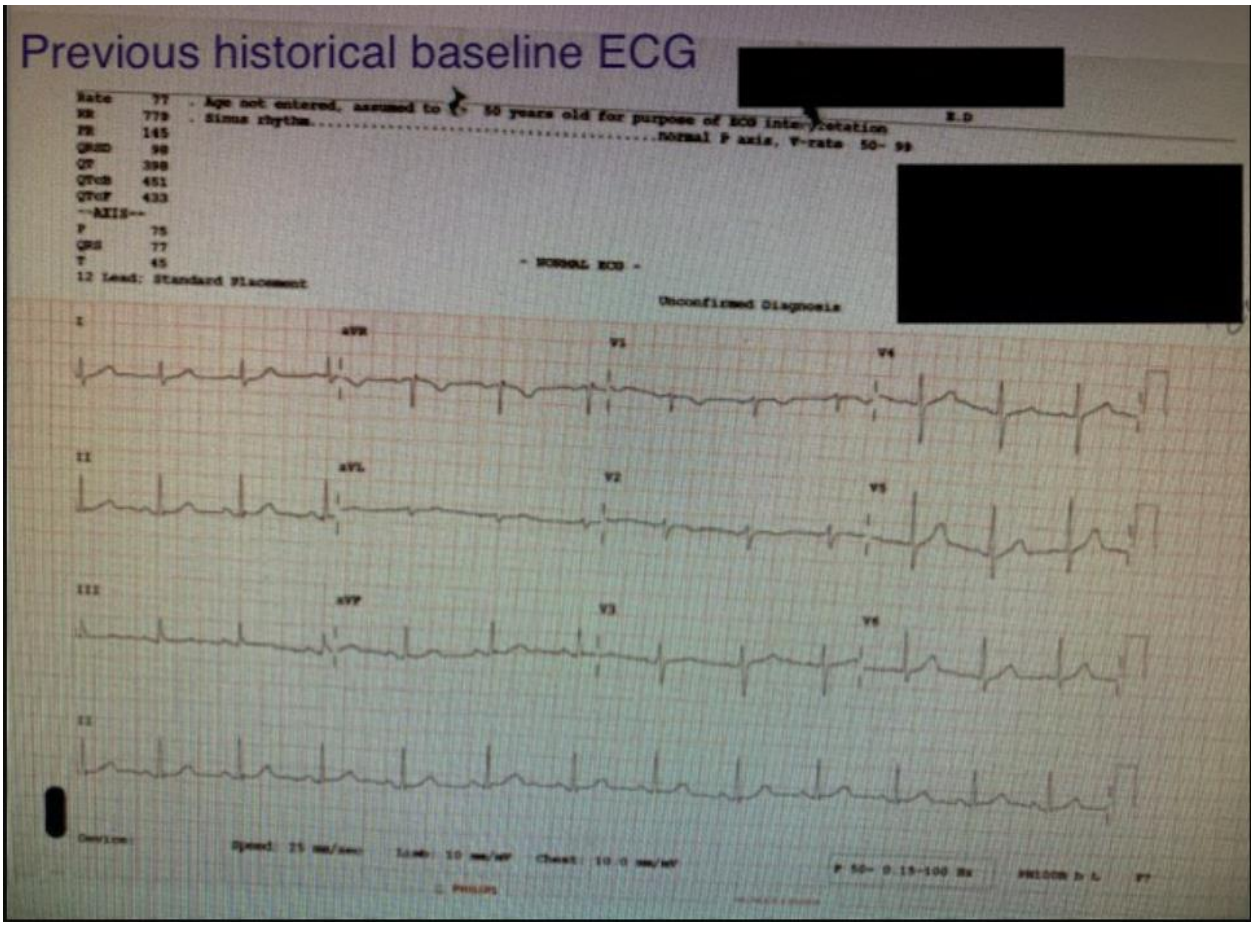

Figure 3: Previous historical documented baseline Electrocardiogram ECG (carried out before 1st admission)

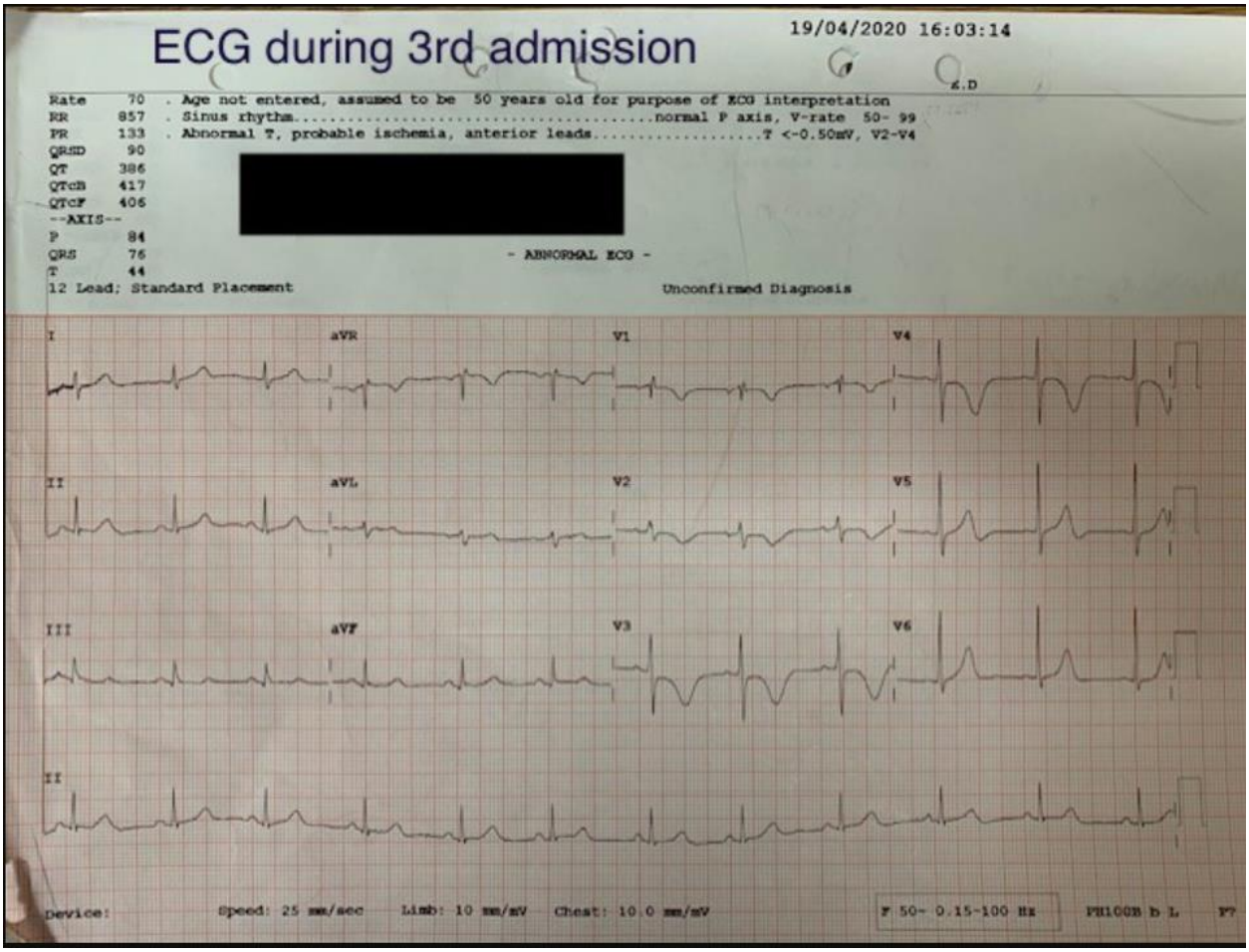

Figure 4: Electrocardiogram (ECG) on 3rd admission showing new T-wave inversion in V2-V5 consistent with possible Wellens Syndrome

Transthoracic echocardiogram (TTE) confirmed normal LV with hypokinesia of anterior septum (new regional wall motion abnormalities/RWMA), normal RV, LA and RA normal size, mild TR, mildly increased PAP 36.1mmHg (+RA), no valves abnormality or pericardial effusion (previous TTE of 19/11/2019 and 17/08/2018 reported normal LV with no regional wall motion abnormalities/RWMA). In view of his on-going anginal chest pains and the new RWMA, he was therefore recommended in-patient urgent Coronary angiography. Coronary angiogram via Right Radial route however showed normal Coronary arteries (***figures 5, 6 and 7- video***).

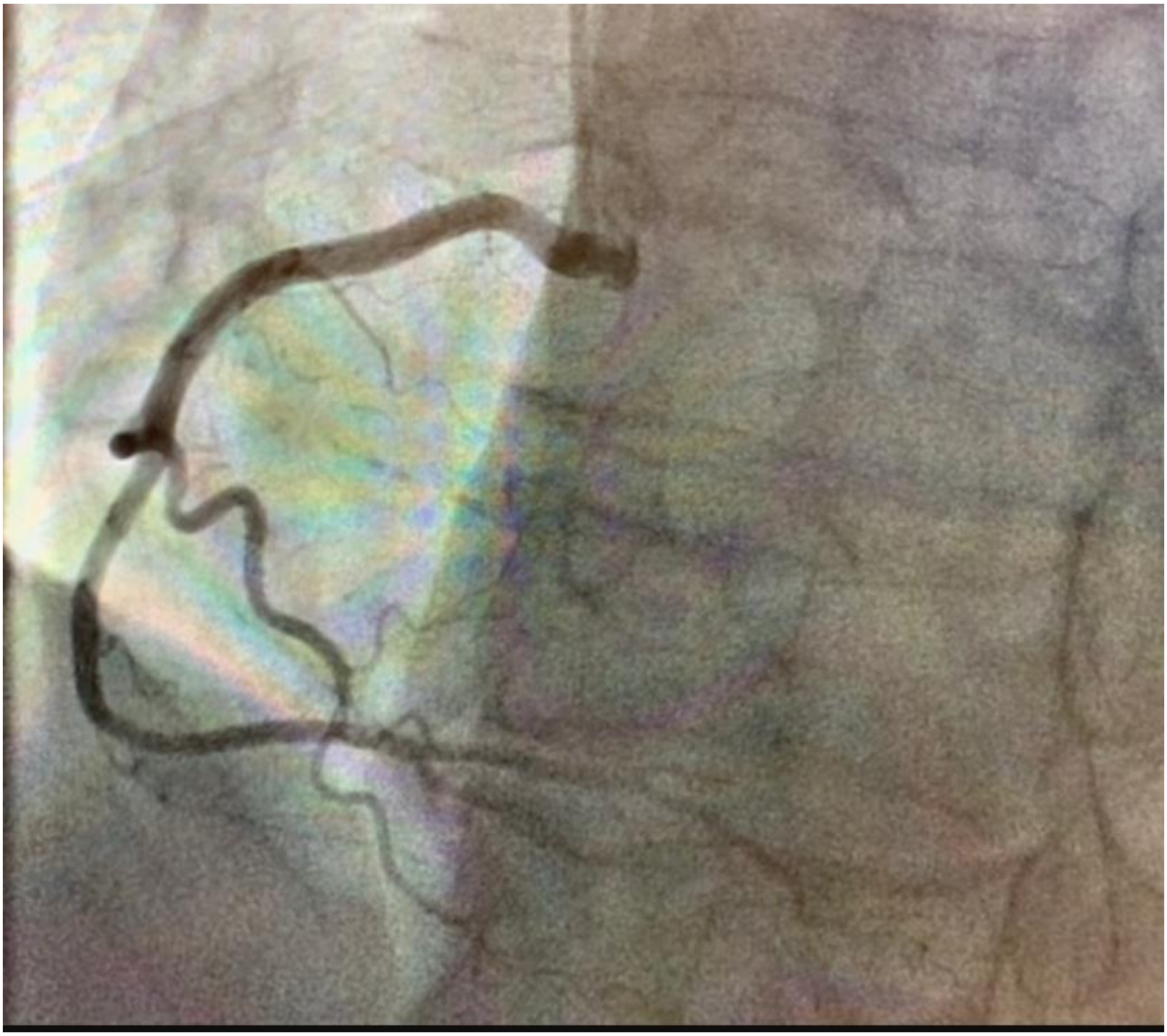

Figure 5: Coronary Angiogram confirming normal anatomy of Right Coronary artery

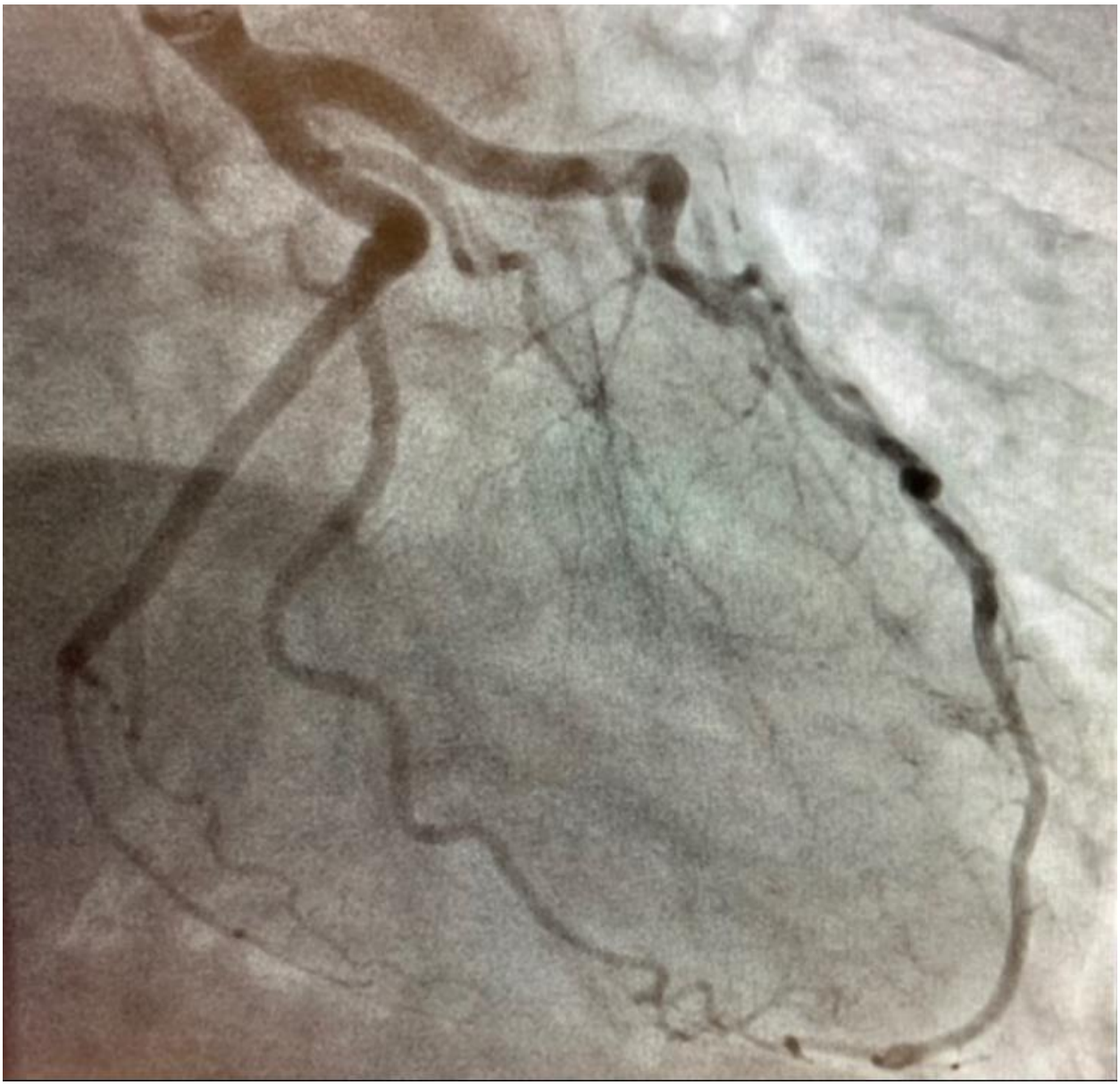

Figure 6: Coronary Angiogram confirming normal anatomy of Left Coronary arteries

Figure 7: Video movie of left coronary system (LMS/LAD/Cx) confirming no evidence of coronary artery disease.

The *final cardiac diagnosis*, presenting as cardiac chest pain, was concluded as most likely recent 'non-coronary' myocardial injury/myocarditis or atypical Takotsubo type cardiomyopathy, which can present as focal isolated hypokinesia of LV segment on TTE, although the precise timing of the cardiac injury would be difficult to elucidate (as no previous TTE was documented). Accordingly, all cardiac ACS medicines (Aspirin, Ticagrelor, Atorvastatin, Ivabradine and Isosorbide mononitrate) were stopped as the LV function was normal and there was no obvious coronary artery disease/arrhythmias. The plan was to follow up in out-patient clinic in 3 months, with repeat TTE and a Cardiac MR. Unfortunately, the patient's sudden death in the community was reported 3 months after discharge (i.e., after 3rd admission).

Discussion:

We report a case, with significant co-morbidity, that was discharged after full recovery from pulmonary COVID-19 infection (repeat negative

COVID-19 swabs, no COVID-19 features on repeat CXR and CTPA) but re-presented within a few days of discharge with 'new cardiac sounding chest pains', 'new ischemic ECG changes in keeping with an initial new provisional diagnosis of Wellens Syndrome (a typical pre-myocardial infarction stage)' [5, 9-12] and 'new regional wall motion abnormalities/RWMA on TTE'. However, subsequent coronary angiogram confirmed normal coronaries, excluding any Wellens Syndrome.

The final presumed cardiac diagnosis therefore was that of a delayed presentation (within 2 weeks of recovery from acute pulmonary COVID-19 infection) following recent 'non-coronary myocardial injury/myocarditis, likely atpical Takotsubo type cardiomyopathy/stress cardiomyopathy. The rationale for such a presumed diagnosis was on the basis of three criteria: a) new and on-going symptoms of cardiac/anginal chest pains on treatment b) ECG changes in keeping with new Wellens syndrome (where cardiac markers might typically be either normal or minimally raised, with only 12 % patients with such ECG changes having significantly raised markers [4, 8-11]), c) findings of the TTE – focal isolated wall motion abnormalities. d) normal coronary angiogram: It is well documented that Wellens syndrome is associated with 100% likelihood of >50% stenosis in the LAD, but in our case presentation, the LAD was normal, again supporting the diagnosis of COVID-19- focal isolated hypokinesia of LV segment on TTE or atypical Takotsubo type cardiomyopathy.

The precise timing of the cardiac injury is difficult to elucidate, with possible sub-clinical cardiac injury at time of initial COVID-19 related admission or shortly after that, with full clinical cardiac presentation at time of 3rd admission. Plausible mechanisms include direct cytokine mediated non-specific cardiac injury/myocarditis, and/or vasculitis/inflammation of the small vessels or even a consequence of the typical hypercoagulable state associated with COVID-19 [9, 12-14], resulting in a ACS/Wellens syndrome-like cardiac presentation and ECG changes. Admittedly, coronary spasm/ Prinzmetals variant angina (PVA) would also remain a potential differential diagnosis [12, 13]. Unlike the previous case report of an assumed Wellens syndrome by Suryawan et al [4], in the current case report we document a normal coronary anatomy to support the final presumed diagnosis. Ideally, however, Cardiac MR scan would have provided much needed diagnostic clarity but local CMR services remained suspended at the time. Unfortunately, the patient's death in the community was recorded 3 months after final discharge, and before he attended for CMR. More recent studies using CMR support similar clinical and even sub-clinical consequences of COVID-19 related cardiac injury [14-18], and potential for future negative consequences.

Finally, whilst the evidence of acute cardiac involvement during active COVID-19 infection [14, 15] with some reports of 'late cardiac presentations' post-respiratory COVID-19 [16-18], this case is the first documented report of atypical Takotsubo type cardiomyopathy with only focal isolated hypokinesia of LV segment with sudden death thereof. Generally, the expectation would be that such isolated and focal cardiac injuries may remain sub-clinical, they carry potential more serious longer-term cardiac consequences including as this case report highlights sudden cardiac death due to COVID-19 related micro/macro myocardial injuries (i.e., scars).

Moreover, cardiac management of such cases also remains challenging especially as the use of conventional cardiac therapies for longer term cardio-protection with preserved LV function is unclear. Likewise, the need and duration for Cardiology follow up would be uncertain. It is therefore plausible that similar to the field of Cardio-Oncology, it might be reasonable for all patients who have survived COVID-19 infection, especially those with high-cardiac risks (elevated cardiac biomarkers or cardiac risk factors) to be offered regular medium (months) to longer-term (years) follow up under Cardiology services to help with early identification of as yet unknown longer-term cardiac consequences including sudden death. Further studies targeting such high-risk patients would therefore be recommended.

Conclusion:

We report a case, with significant co-morbidity, whom was discharged after full recovery from COVID-19 but then presented within a few days with new cardiac symptoms and pathology. This case report highlights the lingering consequences of COVID-19 on the heart, some of which may remain sub-clinical, present clinically after clinical recovery from pulmonary COVID-19 or even with adverse negative consequences (late sudden death). These scenarios offer potential new challenges for cardiologists/services, including consideration for longer-term monitoring/care especially as subsequent post-COVID-19 long term cardiac

sequalae/consequences are as yet unknown. Further studies to screen high-risk patients with elevated cardiac biomarkers or cardiac risk factors post recovery, if not all post-COVID-19 patients, would be of benefit/recommended.

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None

Patient consent statement

Appropriate consent has been obtained in discussions with the patient, and subsequently also in writing (which can be made available when specifically requested).

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Author contributions:

Dr C Read: data collection, interpretation and writing; (c.d.read@doctors.org.uk)
Dr CM Holt: literature search, interpretation and writing; (cathy.holt@manchester.ac.uk)
Prof N Malik: data collection, data analysis, interpretation, literature search and writing

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