Respiratory Medicine Case Reports 32 (2021) 101366

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Myocardial fibrosis after COVID-19 infection and severe sinus arrest episodes in an asymptomatic patient with mild sleep apnea syndrome: A case report and review of the literature

Christos E. Lampropoulos [a,*], Sophie Mavrogeni [b], Agisilaos Dervas [c], Efstathios Manios [d], Sofia Chatzidou [d], Christos Kontogiannis [d], Sotiria Spiliopoulou [d], Stamatoula Melliou [d], Emmanouela Kalogianni [d], Ioanna Papaioannou [a]

[a] Emergency Department, "Alexandra" General Hospital, Athens, Greece
[b] Onassis Cardiac Surgery Center, Athens, Greece
[c] Pulmonologist - Somnologist, Sleep Laboratory Department, Henry Dunant Hospital Center, Athens, Greece
[d] Department of Clinical Therapeutics, School of Medicine, "Alexandra General Hospital", Athens, Greece

ARTICLE INFO

Keywords:
COVID-19 infection
Myocardial fibrosis
Sinus arrest
Obstructive sleep apnea syndrome

ABSTRACT

COVID-19 infection is a new disease mainly affecting the respiratory system but is also accompanied by many extra-pulmonary manifestations. A case of a 47-year old male with unique myocardial fibrosis after COVID-19 infection involving the left ventricular wall, intraventricular septum and almost complete damage of interatrial septum, in combination with asymptomatic severe sinus arrest episodes related to mild obstructive sleep apnea syndrome is described here.

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic has emerged as a global health problem with incalculable consequences. The high transmission capacity of the virus has led to worldwide expansion of the disease, affecting all aspects of human life.

The major manifestations of the disease concern the respiratory system with a not negligible percentage of serious complications necessitating admission to intensive care unit. Nevertheless, a significant number of patients manifest extra-pulmonary symptoms, such as from the cardiovascular system. Myocarditis, myocardial infarction, stroke, heart failure and ventricular arrhythmias (either as a consequence of myocardial injury or due to treatment-related QT prolongation) are well established complications with significant impact on patients' quality of life, morbidity and mortality [1]. Patients with pre-existing cardiovascular disease (CVD) represent a high-risk group for developing even more severe form of the disease [2].

Arrhythmiogenesis is a well documented complication of obstructive sleep apnea (OSA) syndrome. Autonomic nervous system (ANS) imbalance between vagal tone and sympathetic activity may contribute to the development of cardiac rhythm disorders, either tachy- or brady-arrhythmias. Sleep apnea-induced hypoxemia appears to be the key mechanism for the increased vagal tone and bradycardic rhythm disorders. Dangerous or significant arrhythmias usually occur in patients with moderate or severe form of OSA whereas in mild form they tend to be more benign.

A case of a patient with significant myocardial fibrosis, without any cardiac symptoms, after COVID-19 infection in combination with asymptomatic severe sinus arrest (SA) episodes related to mild OSA is described here.

2. Case report

A 47-year old male presented 4 months ago in the emergency department with low-grade fever (37.5 °C) and intense exhaustion the last 2 days. He mentioned no symptoms from respiratory or gastrointestinal system, headache, rash or arthralgiae. His medical history included only Hashimoto's thyroiditis, regularly evaluated and well controlled with 125μg of levothyroxine. He was overweighed (body mass index = 29 kg/m^2), with no smoking habits or alcohol abuse. He did not report any episode of unexplained fever in the past. Clinical evaluation was normal except detection of fever (37.8 °C). Lungs' x-ray

* Corresponding author. P. P. Germanou 28, Halandri, 15233, Athens, Greece.
E-mail address: christosnina@hotmail.com (C.E. Lampropoulos).

https://doi.org/10.1016/j.rmcr.2021.101366
Received 28 November 2020; Accepted 13 February 2021
Available online 17 February 2021

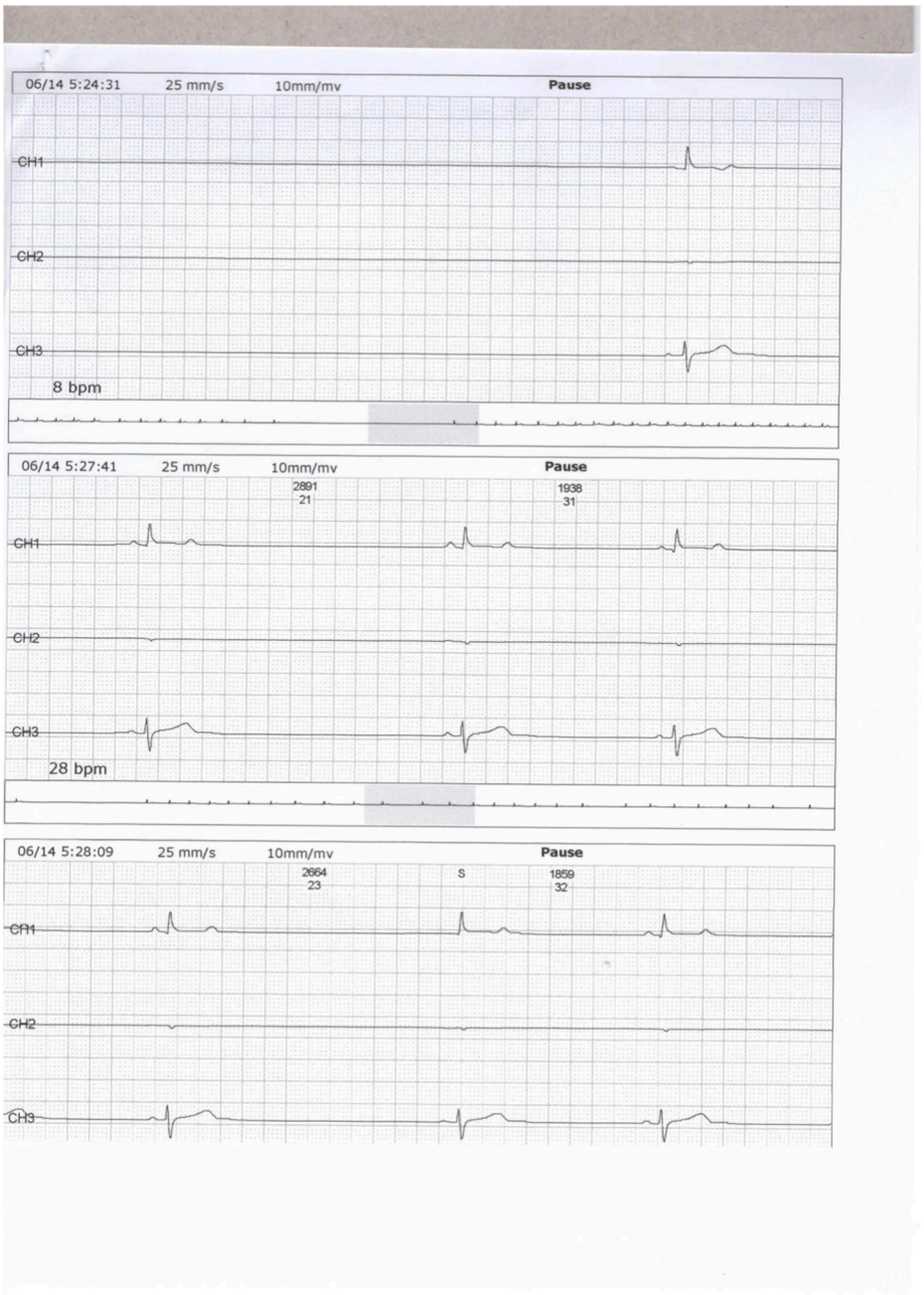

Fig. 1. Holter rhythm recording of sinus arrest episode of 13 seconds duration.

and blood tests including inflammatory markers were normal and COVID-19 infection was confirmed with reverse transcription-polymerase chain reaction (RT-PCR) swab test (very high viral load according to our national laboratory). Treatment including hydroxychloroquine (HCQ, 800mg/day the first 2 days followed by 400mg/day) and azithromycin (500mg/day) was immediately initiated, according to the national guidelines. Nevertheless, his symptoms deteriorated after the 5th day of treatment with high fever (up to 38.5 °C), intense non-productive cough and dizziness and he was admitted to the reference hospital. Lungs' auscultation revealed a few bilateral rales whereas in laboratory investigation only marginally elevated C-reactive protein was found (0.7mg/dL, reference value $<$ 0.5mg/dL). A new lung x-ray was normal and computed tomography (CT) showed scattered, small ground-glass opacities, mainly in the periphery of the lungs. Oxygen saturation (sO_2) was stable (97%) except for the first day of admission (95%). Treatment duration was extended to 10 days for HCQ and 6 days for azithromycin and the patient became afebrile after the 9th day. He was discharged 3 days later and remained in isolation for 50 days totally due to continuously positive RT-PCR tests. Anti-COVID-19 antibodies were strongly positive three months after disease presentation (IgG = 9.32 and IgA$>$13, reference value $<$ 0.8).

All this period the patient was complaining for significant exhaustion even with minimal activities, a symptom that was attributed to the viral infection and the extended period of restriction. After invitation he participated in a national survey for detecting cardiovascular complications due to COVID-19. The survey included doppler echocardiography as well as holter blood pressure and rhythm monitoring. While no significant abnormalities were found in the first 2 examinations, the findings of the last one were quiet impressive. Periods of sinus bradycardia were detected during sleep [minimum heart rate (HR) 16 beats per minute (bpm)] with many episodes of SA (maximum duration of 9.08 seconds). Holter was repeated for 5 consecutive days with even

Table 1
Quantitative analysis of ventricles' myocardial function.

	Left Ventricle	Right Ventricle
Ejection fraction	62.5%	56.3%
Stroke volume	101.2 ml	87.9 ml
Cardiac output	5.6 lt/min	5 lt/min
End-diastolic volume	161.7 ml	156.4 ml
End-systolic volume	60.5 ml	68.4 ml
End-diastolic mass	139.6 gr	

more striking results: 98 episodes of SA (>2 seconds) were recorded in 24h with maximum duration of 13 seconds (Fig. 1). All bradycardic episodes were recorded during sleep, while no electrocardiographic abnormalities were recorded during the day. No other arrhythmias were detected such as premature complexes, brady/tachyarrhythmias, ventricular arrhythmias or atrioventricular block. The patient denied any symptoms relevant to significant bradycardia (syncope, dizziness) or OSA (daytime somnolence, snoring, frequent sleep awakening).

The patient underwent immediately a polysomnographic evaluation in order to estimate the possible effect of OSA on SA. The total duration of sleep was 379 minutes, duration of snoring was 4.6 minutes and the apnea/hypopnea index was 12.3/h. Mean sO_2 was 93% while duration of low oxygen (sO_2 <90%) was 0.5 minutes. Mean HR was 54bpm with bradyarrhythmias during episodes of apnea/hypopnea.

Despite the normal doppler echocardiography the patient was advised to perform cardiac magnetic resonance imaging (MRI) in order to detect any structural myocardial abnormalities. The MRI was performed using a 3T system (Skyra, Siemens). The short and long axis steady-state free precession (SSFP) images were obtained to assess myocardial function (Table 1). T2 ratio, calculated from signal intensity of myocardium over the signal of latissimus dorsi, T2 mapping and early gadolinium enhancement were within normal limits excluding the presence of acute, active myocardial inflammation. However, the late gadolinium enhanced (LGE) images showed evidence of subepicardial fibrosis in the lateral wall of left ventricle (LV), subendocardial fibrosis in the apical part of intraventricular septum and transmural fibrosis involving more than 2/3 of the atrial septum (Fig. 2). The total amount of fibrosis was 6% of LV mass.

Because of this unique pattern of myocardial fibrosis, the patient was further evaluated by rheumatologists for underlying connective tissue diseases (CTD) that could affect myocardium. However, all immunological investigation was negative. A new lungs' CT was completely normal. The patient underwent an exercise tolerance test for 12 minutes with normal variation of all recorded parameters.

As the SA episodes, though significant, were detected only during the sleeping procedure and there were no signs of sinus node dysfunction, the patient was advised to start continuous positive airway pressure (CPAP) treatment and re-evaluated again after 3 months in order to decide the placement of a permanent pacemaker.

3. Discussion

Cardiovascular manifestations are a feared complication of COVID-19 infection carrying worse prognosis and high mortality. Cardiac involvement has been attributed to multiple mechanisms and patterns of injury. It has been suggested that the virus can directly affect myocardium with macrophage infiltration and inflammation [3,4]. Elevated troponin levels are present in up to 20% of hospitalized patients revealing myocardial involvement and are also related with higher ventricular arrhythmia risk [5,6].

Cardiac MRI is a sensitive tool for early detection of heart damage. Major MRI findings include myocardial edema, fibrosis, infarction, pericarditis and impaired ventricles' function. Myocardial fibrosis is a consequence of tissue injury and can be detected as LGE on MRI. It seems that the location of tissue damage by COVID-19 is slightly differentiated from that caused by other acute viral myocarditis as it commonly involves interventricular septum and the anterior wall [7,8]. Although myocarditis typically affects the ventricles, the atrium may also be

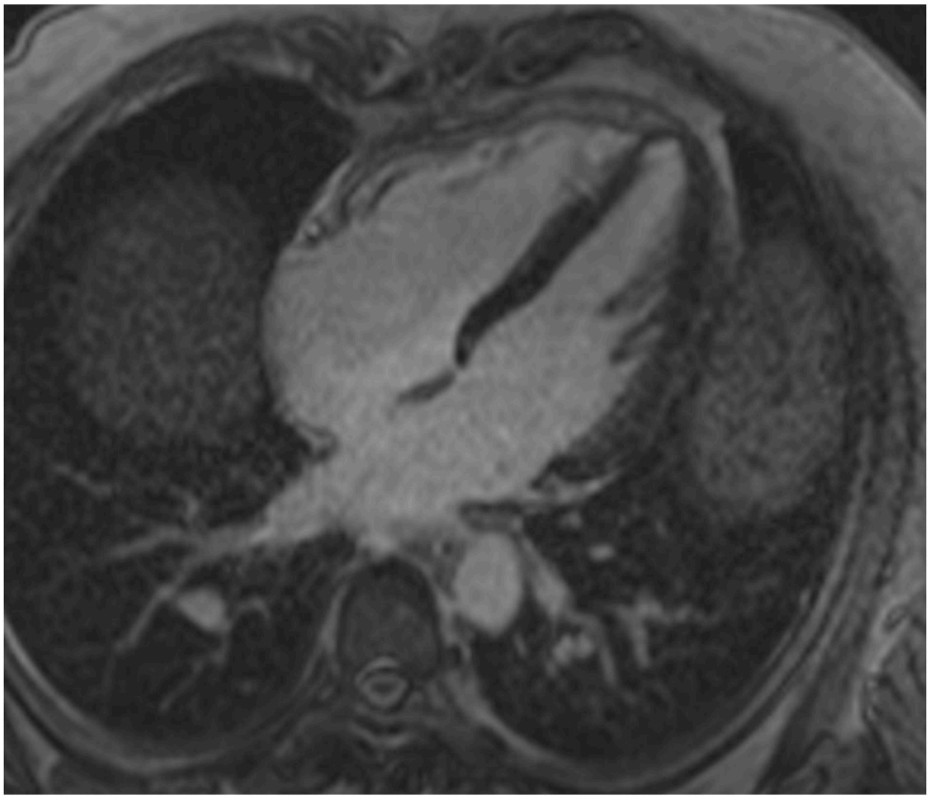

Fig. 2. Late gadolinium enhanced image with fibrosis of left ventricular wall, intraventricular and interatrial septum.

involved [9]. Our patient had a unique myocardial involvement with almost total replacement of normal interatrial septal tissue by fibrotic one, a finding that has never been described before. As the patient was completely healthy in the past, someone could suggest that these MRI findings can be attributed to COVID-19 infection. Literature review for diseases, such as viral/bacterial infections or CTD that may affect the heart did not reveal any similar pattern of fibrosis [10,11]. On the other hand, significant cardiac involvement may occur independently of the severity of disease and persists beyond the period of acute presentation [12].

Arrhythmias are not uncommon in patients suffering from COVID-19 [13]. Malignant ventricular tachycardia is the most feared complication, atrial fibrillation is more common in patients receiving mechanical ventilation whereas sudden cardiac death has been reported in patients with mild symptoms of the disease [14,15]. Sinus bradycardia may be detected in some patients and it disappears when viral nucleic acid tests turn negative, irrespective of patients' condition [16]. Hydroxychloroquine treatment is a causative factor for QT prolongation, torsades de pointes and sudden death [17]. The episodes of SA in our patient are exclusively related with sleeping procedure, though very unusual and serious for such mild OSA syndrome, making impossible the correlation with the viral infection. Nevertheless, the coexistence of two unrelated serious manifestations in the same patient makes the presentation of this case report impressive. The patient is currently under CPAP treatment as the need for pacemaker implantation is still under debate for patients without daytime symptoms or cardiac conduction system abnormalities [18–20].

4. Conclusions

COVID-19 infection is a new entity with undefined, yet, long-term complications. New data appear daily expanding the range of manifestations of the disease. The persistence of patient's discomfort may require exhaustive investigation in order to arrive at a diagnosis. Cardiac MRI has an important role in identifying silent fibrosis that can potentially influence patients' risk stratification and treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of competing interest

None.

References

[1] R.D. Mitrani, N. Dabas, J.J. Goldberger, COVID-19 cardiac injury: implications for long-term surveillance and outcomes in survivors, Heart Rhythm (2020), https://doi.org/10.1016/j.hrthm.2020.06.026. S1547-5271(20)30625-1.

[2] Y. Kang, T. Chen, D. Mui, V. Ferrari, D. Jagasia, M. Scherrer-Crosbie, et al., Cardiovascular manifestations and treatment considerations in COVID-19, Heart 106 (2020) 1132–1141.

[3] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med. 46 (2020) 846–848.

[4] G. Tavazzi, C. Pellegrini, M. Maurelli, M. Belliato, F. Sciutti, A. Bottazzi, et al., Myocardial localization of coronavirus in COVID-19 cardiogenic shock, Eur. J. Heart Fail. 22 (2020) 911–915.

[5] P.K. Bhatraju, B.J. Ghassemieh, M. Nichols, R. Kim, K.R. Jerome, A.K. Nalla, et al., Covid-19 in critically ill patients in the Seattle region—case series, N. Engl. J. Med. 382 (2020) 2012–2022.

[6] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 811–818.

[7] J.A. Luetkens, J. Doerner, D.K. Thomas, D. Dabir, J. Gieseke, A.M. Sprinkart, et al., Acute myocarditis: multiparametric cardiac MR imaging, Radiology 273 (2014) 383–392.

[8] L. Huang, P. Zhao, D. Tang, T. Zhu, R. Han, C. Zhan, et al., Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging, JACC Cardiovasc. Imag. S1936–878X (20) (2020) 30403–30404, https://doi.org/10.1016/j.jcmg.2020.05.004.

[9] M.P. Begieneman, R.W. Emmens, L. Rijvers, B. Kubat, W.J. Paulus, A.B. Vonk, et al., Ventricular myocarditis coincides with atrial myocarditis in patients, Cardiovasc. Pathol. 25 (2016) 141–148.

[10] S. Mavrogeni, P.P. Sfikakis, E. Gialafos, K. Bratis, G. Karabela, E. Stavropoulos, et al., Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases, Arthritis Care Res. 66 (2014) 104–112.

[11] S. Mavrogeni, C. Bratis, M. Manoussakis, Coronary artery abnormalities in CREST syndrome revealed by cardiovascular magnetic resonance imaging, Can. J. Cardiol. 27 (2011), 390.e5-7.

[12] V.O. Puntmann, L. Carerj, I. Wieters, M. Fahim, C. Arendt, J. Hoffmann, et al., Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020), e203557, https://doi.org/10.1001/jamacardio.2020.3557.

[13] M. Boukhris, A. Hillani, F. Moroni, M.S. Annabi, F. Addad, M.H. Ribeiro, et al., Cardiovascular implications of the COVID-19 pandemic: a global perspective, Can. J. Cardiol. 36 (2020) 1068–1080.

[14] C. Lazaridis, N.I. Vlachogiannis, C. Bakogiannis, I. Spyridopoulos, K. Stamatelopoulos, I. Kanakakis, et al., Involvement of cardiovascular system as the critical point in coronavirus disease 2019 (COVID-19) prognosis and recovery, Hellenic J. Cardiol. (2020), https://doi.org/10.1016/j.hjc.2020.05.004. S1109-9666(20)30093-2.

[15] A.N. Kochi, A.P. Tagliari, G.B. Forleo, G.M. Fassini, C. Tondo, Cardiac and arrhythmic complications in patients with COVID-19, J. Cardiovasc. Electrophysiol. 31 (2020) 1003–1008.

[16] L. Hu, L. Gong, Z. Jiang, Q. Wang, Y. Zou, L. Zhu, Clinical analysis of sinus bradycardia in patients with severe COVID-19 pneumonia, Crit. Care 24 (2020) 257.

[17] L. Jankelson, G. Karam, M.L. Becker, L.A. Chinitz, M.C. Tsai, QT prolongation, torsades de pointes and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review, Heart Rhythm 17 (2020) 1472–1479.

[18] W. Grimm, U. Koehler, E. Fus, J. Hoffmann, V. Menz, R. Funck, et al., Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy, Am. J. Cardiol. 86 (2000) 688–692.

[19] E.N. Simantirakis, S.I. Schiza, M.E. Marketou, S.I. Chrysostomakis, G. I. Chlouverakis, N.C. Klapsinos, et al., Severe bradyarrhythmias in patients with sleep apnea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder, Eur. Heart J. 25 (2004) 1070–1076.

[20] S. Garrigue, P. Bordier, P. Jais, D.C. Shah, M. Hocini, C. Raherison, et al., Benefit of atrial pacing in sleep apnea syndrome, N. Engl. J. Med. 346 (2002) 404–412.