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New onset of ventricular arrhythmia in convalescent coronavirus disease 2019 patient

Nowo wykryta arytmia komorowa u ozdrowieńca po chorobie koronawirusowej 2019

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Abstract

Cardiac complications are counted among the complications of coronavirus disease 2019 (COVID-19) in hospitalized patients. However, the data of non-hospitalized COVID-19 convalescents' population is scant. This study presents a case of a 42-year-old woman with no medical history who underwent SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) infection at 16 March 2020. She had a fever (38 degrees Celsius) and dyspnoea that resolved after chloroquine administration so the patient was not hospitalized. One week later she reported palpitations and fatigue of functional class II New York Heart Association despite negative repeated polymerase chain reaction results (23rd March, 1st April). Within 6 weeks she was referred to a cardiologist. The laboratory test results revealed slightly increased high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide. On electrocardiogram (ECG), single ventricular extrasystoles of right bundle branch block shape were observed. 24-hrs ECG Holter monitoring revealed additionally symptomatic periods of bigeminy and 4.2 thousands of ventricular extrasystoles. The cardiac magnetic resonance showed typical post-inflammatory myocardial changes with no active inflammation. No pharmacotherapy was applied. The symptoms have ceased. In the 4th month, 24-hrs ECG Holter revealed the recovery from arrhythmia. The presented case showed that long-term medical observation is worth to be considered even for non-hospitalized patients with a mild course of SARS-CoV-2 infection.

Key words: SARS-CoV-2 infection, arrhythmia, myocarditis, non-hospitalized convalescent

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Introduction

In the pandemic target of research is to evaluate cardiovascular (CV) effects. Among coronavirus disease 2019 (COVID-19) hospitalized patients in 7–23% developed a myocardial injury. Its symptoms vary from mild manifestation such as fatigue or dyspnea, through chest pain or tachycardia, up to cardiogenic shock or sudden cardiac death [1]. Yet, the late manifestation of COVID-19 CV sequelae has been noticed [2, 3]. They are presumed to be caused by cytokine storm as in other viral infections. The precise number of previously hospitalized COVID-19 patients with cardiac complications is unknown. However, the bigger is non-hospitalized COVID-19 population and the long-term data of non-hospitalized COVID-19 survivors including cardiac complication is still missing [4].

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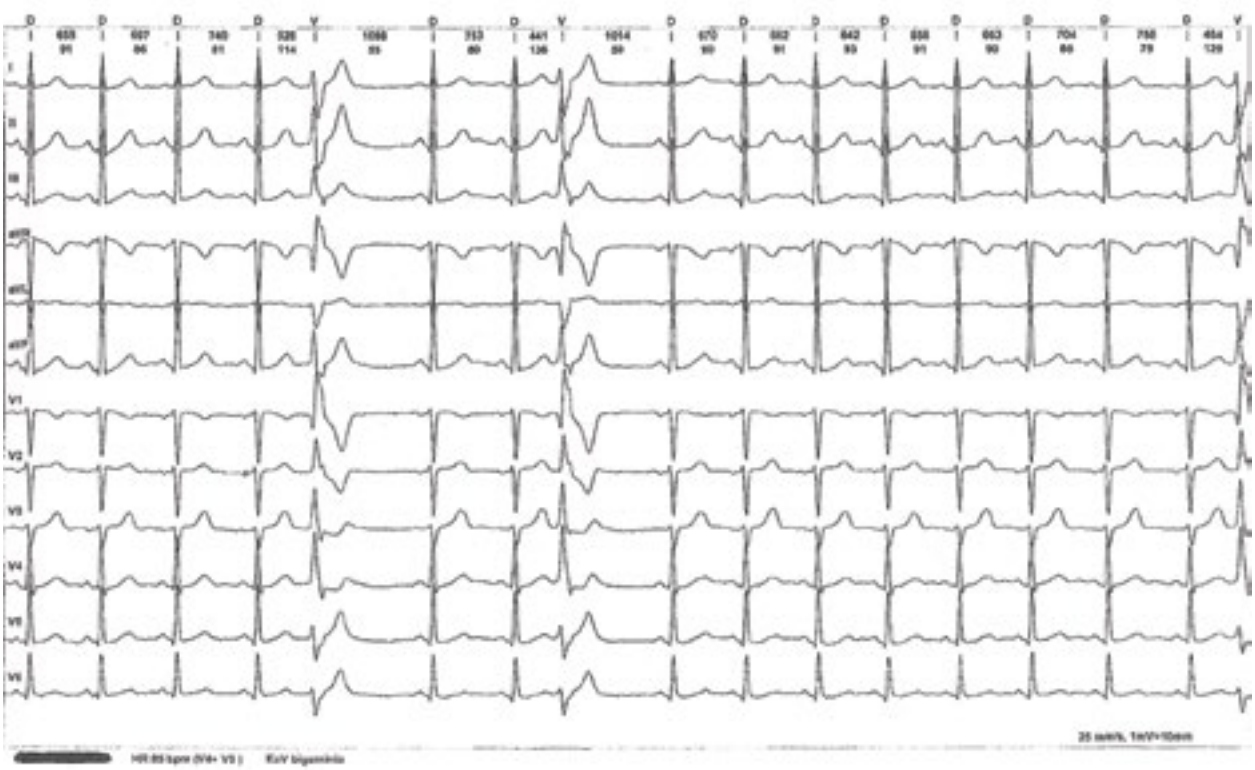

Figure 1. 24-hrs electrocardiogram (ECG) Holter — single ventricular extrasystoles of right bundle branch block shape

Case report

A 42-year-old female patient with no medical history underwent SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) infection at 16st March 2020 (polymerase chain reaction [PCR] positive result). The patient had a fever (38 degrees Celsius) and dyspnoea. Chloroquine was administered for 6 days — 500 mg/day, with significant clinical improvement (resolution of dyspnoea and fever). She was not hospitalized. One week later there was the onset of palpitations, fatigue, and functional class II New York Heart Association (NYHA). However, PCR results were twice negative (23rd March, 1st April).

After 6 weeks she was referred to a cardiologist due to dyspnoea and palpitations. The outcomes of laboratory tests revealed slightly increased concentration of high-sensitivity cardiac troponin T (hs-cTnT) 32 ng/L (norm 9–22 ng/L) and natriuretic peptide [N-terminal pro-B-type natriuretic peptide (NT-proBNP)] 184 pg/mL (norm ≤ 125 pg/mL). The other laboratory parameters were in normal ranges, including lymphocytes 2.13 × 10^3 μL, C-reactive protein (CRP) — 28.3 nmol/L (norm ≤ 76.19 nmol/L) and D-dimer — 230 μg/L (norm < 500 μg/L).

On electrocardiogram (ECG) at rest, single ventricular extrasystoles of right bundle branch block shape were present. 24-hrs ECG Holter monitoring revealed sinus rhythm, 4.2 thousands of ventricular extrasystoles with symptomatic periods of bigeminy and also 597 single supraventricular extrasystoles (Figure 1).

The pulmonary computed tomography (CT) did not detect any abnormalities. However, the cardiac magnetic resonance (CMR), performed 60 days after positive PCR, showed the late mesocardial and subepicardial enhancement typical of myocarditis but without signs of active inflammation (Figure 2). Left ventricular ejection fraction was 64%. The patient had no pharmacotherapy.

On the second visit after 3 months from positive PCR, the patient reported alleviation of palpitation. In the 4th month, 24-hrs ECG Holter monitoring revealed the recovery from ventricular arrhythmia.

Control CMR was scheduled to be performed within 6 months.

Discussion

The major part of literature about COVID-19 is considering solely the hospitalized population and is mostly focused on acute respiratory syndrome and multiorgan dysfunction [5]. Nevertheless, the CV complications of SARS-CoV-2 infection are gaining more and more medical attention (Table 1) [6].

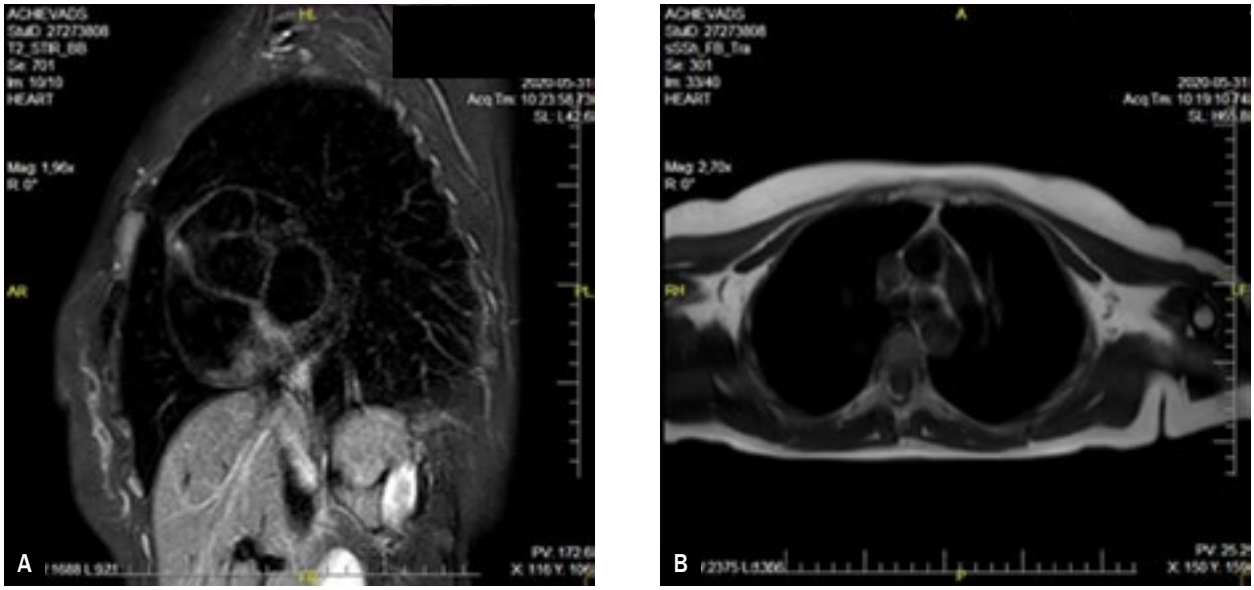

Figure 2A, B. Cardiac magnetic resonance — late gadolinium-enhanced images in sagittal and frontal planes: mesocardial enhancement of basal and middle intraventricular septum segments and also subepicardial enhancement of basal and middle parts of the inferior myocardial segment between right and left ventricle

While hypertension, diabetes and coronary artery disease are associated with poor COVID-19 prognosis, Polish authors [7] have recently observed that only senior age, CRP and National Early Warning Score (NEWS) ≥ 2 were risk factors for death in patients with comorbidities. On the other hand, Chinese author [8] reported that fulminant myocarditis could cause even 7% of COVID-19-related deaths but the ratio may be overestimated due to lack of confirmatory diagnoses. Although the majority of studies is referring to acute conditions associated with coexisting CV risk factor or disease, the cases of myocardial injury without previous CV history are also reported. In general, any comorbidities are suspected to increase the risk of hospitalization in patients with COVID-19, but it remains uncertain whether they emphasize patients' susceptibility to infection or not [9]. Moreover, the incidence of myocardial injury seems to be comparable both in patients with high and with a low prevalence of pre-existing CV disease [10].

Table 1. Cardiac outcomes in hospitalized coronavirus disease 2019 (COVID-19) patients based on meta-analysis (by Kunutsor et al. [10])

Complication	Number of included studies (number of patients)	Pooled incidence [%]
ACS	2 (N = 101)	6.2
Arrhythmia	6 (N = 867)	9.3
Cardiac arrest	2 (N = 187)	5.7
Cardiac injury	11 (N = 2,028)	16.3
DIC	2 (N = 359)	5.6
HF	4 (N = 820)	17.6

ACS — acute coronary syndrome; DIC — disseminated intravascular coagulation; HF — heart failure

At least, there is insufficient information about possible sequelae or treatment of non-hospitalized patients with a mild course of COVID-19. Though, it is supposed that almost 30% of these patients may need subsequent hospitalization [11]. Additionally, pulmonary embolism (PE) seemed to be the most studied COVID-19 complication in outpatients. Alharthy et al. [12] reported two cases of non-hospitalized asymptomatic patients during SARS-CoV-2 infection who presented with PE 20 and 35 days later. Similarly, Gervaise et al. [13] identified CT scans finding PE in 18% of 72 non-hospitalized patients.

Documented cases of myocarditis caused by COVID-19 in patients without prior pneumonia or those who overcome COVID-19 indicate the risk of late-onset of cardiac complications, regardless of the severity of the COVID-19 symptoms [2]. The course of myocarditis can be mild to severe, or even fulminant and requiring a heart transplant. Furthermore, it is important to remember that COVID-19 symptoms may impose symptoms of myocarditis in course of COVID-19 [1].

COVID-19 related myocardial injury should be suspected in elevated troponins, as Inciardi et al. [2] presented in their case of a 53-year-old woman. The patient showed a positive PCR test for COVID-19 and was admitted to the cardiac care unit. She reported severe fatigue 2 days before the hospitalization as well as having high fever and cough that occurred the week before. However, she denied

chest pain, dyspnoea and further cardiovascular symptoms. Myocarditis was confirmed on CMR a week after the onset of symptoms and was accompanied by an increased level of NT-proBNP (5647 pg/mL; reference range < 300 pg/mL) and hs-cTnT level (0.24 ng/mL; reference range < 0.01 ng/mL) at admission. At the time of CMR performing the level of hs-cTnT was 0.63 ng/mL. On the other hand, Huang et al. [14] reported in 26 young patients, from who 22 recovered from moderate COVID-19 pneumonia, the results of troponin levels and CMR. Among this population only 8% of patients had prior CV history, 88% presented palpitation at admission. Surprisingly, only half of the patients had elevated hs-cTnI during hospitalization, which has normalized at the time when CMR was performed, an average of 47 days [interquartile range (IQR): 36 to 58 days] from symptoms onset and signs of myocardial injuries, such as increased T2 signal and/or positive LGE were presented in 15 (58%) patients. In 14 (54%) patients myocardial oedema was identified as a symptom of an active inflammatory process.

It is well known that troponin is elevated in a large number of diseases and also in the multiorgan complication in COVID-19, so in myocardial injury the gold standard is CMR. Puntmann et al. [3] in the first prospective observational cohort study of 100 unselected COVID-19 survivors identified from the University Hospital Frankfurt COVID-19 Registry, who underwent mild or moderate COVID-19, reported in 67% no need of hospitalization, and screened the patients for the presence of myocardial injury. The median time interval between COVID-19 diagnosis and CMR with T1 and T2 mapping was 71 days. A number of 78 patients lately recovered from COVID-19 occurred to have abnormal CMR results, including at least one of the following: raised myocardial native T1 (N = 73), raised myocardial native T2 (N = 60), myocardial LGE (N = 32), or pericardial enhancement (N = 22). On a contrary to Huang et al. study, 71% of patients had elevated troponin (median 4.9 pg/mL, IQR 3.0 to 6.9 pg/mL) at the time of CMR. Importantly, compared with a healthy control group and CV risk-factors matched controls, the patients who underwent COVID-19 infection, presented lower left ventricular (in mean 57%) and right ventricular (in mean 54%) ejection fraction. CMR occurs to be a quantitative method allowing to determine the percentage of myocardial damage (mapping T1 and T2), repeatable, valuable for monitoring the course of the disease and the effects of therapy. Local fibrosis detected by late gadolinium enhancement (LGE) is a common finding in patients who have had viral myocarditis. Gräni et al. [15] found that the risk of the following CV complications was slightly altered by the presence of LGE with annual CV events [hazard ratio (HR): 2.22; 95% confidence interval (CI): 1.47 to 3.35; p < 0.001]. Subsequently, inflammation and fibrosis of the myocardium may take part in disease progression to heart failure (HF). The data on COVID-19 related myocarditis is still limited. However, considering the inflammatory nature of COVID-19 together with the myocardial inflammation and myocardial fibrosis as HF pathogenesis, future development of HF is expected. Therefore, appropriate heart imaging techniques must be implemented.

Viral infections are considered possible triggers of myocarditis and consequently of arrhythmias [9]. Two pathophysiologic mechanisms are described in myocarditis due to SARS-Cov-2 infection: the cytokine storm and the virus affinity for angiotensin-converting enzyme 2 (ACE2) [1]. Although transmembrane ACE2 allows the virus to invade host cells including endothelial cells and pericytes that may result in endothelitis and important microvascular or macrovascular dysfunction [9]. Attention is drawn mostly to fulminant myocarditis with no initial respiratory symptoms and with rapid clinical progression requiring hospitalization [16–18]. Hu et al. [16] described a case of acute HF due to fulminant myocarditis in a 37-year-old man without comorbidities, whose levels of hs-cTnT was more than 10,000 ng/L and NT-proBNP of 21,025 ng/L. Additionally, his left ventricular ejection fraction was 27%. He was successfully treated with methylprednisolone and immunoglobulin. Whereas, Paul et al. [17] reported a case of acute myocarditis as the main manifestation of COVID-19 in a 35-year-old man without comorbidities, who presented with a level of hs-cTnT up to 2,885 ng/L and typical image of myocarditis in CMR even though his systolic function was normal and there was no pericardial effusion. Simple cardiological treatment with ramipril and bisoprolol sufficed for the patient's recovery. Any of the authors, however, did not mention the patient's follow-up. It is thought that important serum troponin elevation in course of SARS-CoV-2 infection might be related as well to myocardial injury as to multiple organ damage. Thus, neither hs-cTnT nor NT-proBNP is sufficient in diagnosing of myocarditis [1]. Nevertheless, for elevated troponin levels the risk of in-hospital mortality induced by COVID-19 increases 4 times [19]. Other biomarkers warning about significant COVID-19 complications are among others increased lactate dehydrogenase (LDH) level in case of secondary liver damage or increased creatinine level and decreased glomerular filtration rate in case of secondary kidney damage [4]. The details of biomarkers in COVID-19 are summarized in the expert opinion of the Heart Failure Working Group of the Polish Cardiac Society [4].

In the more advanced clinical stage of myocardial injury in myocarditis as a cardiac shock, the American Heart Association (AHA) guidelines [20] and other statements of the experts suggest that in initial management inotropes and vasopressors as well as mechanical ventilation need to be administered. However, the usage of intravenous immunoglobulins, as well as corticosteroids, is not recommended

Table 2. Potential coronavirus disease 2019 (COVID-19) therapies

Theraphy	Effectiveness	Method of administration	Number of tested	ClinicalTrails.gov Identifier	Cardiovascular side effects
Remdesivir	Most promising anti-viral medication	Intravenous	4891 1113	NCT04292899 NCT04292730	Unknown
Tocilizumab	Testing not promising	Intravenous	450	NCT04320615	Hypertension Hyperlipidaemia
Corticosteroids (dexamethasone)	Recommended only if severe/critical COVID-19	Intravenous	482	NCT04381936	Dyslipidaemia Hypertension
Covalescent plasma	Beneficial among infected patients	Intravenous	35322	NCT04338360	Thrombotic events
Lopinavir/ritonavir	Not satisfactory	Oral	1596	NCT04381936	Concomitant administration of QT- or PR-prolonging agents Ischaemic heart disease

on account of their inefficiency in myocarditis [21]. Whereas, the described case in this report provided arrhythmia in course of subacute myocarditis as a mild secondary inflammatory response to SARS-CoV-2 infection with no need for pharmacotherapy.

In the meantime, work is still underway to improve COVID-19 vaccines. The first vaccine available on the market was the Pfizer-BioNTech COVID-19 Vaccine® authorized by the U.S. Food and Drug Administration (FDA) for emergency use under an Emergency Use Authorization (EUA) to prevent COVID-19 for use in individuals of minimum 16 years-old. The *in vitro* capacity of sera immunized with the Pfizer-BioNTech COVID-19 Vaccine® for neutralization of SARS-CoV-2 with key mutations present in the United Kingdom (U.K.) and South Africa variants has been recently studied and the preliminary results are promising [22].

The treatment of SARS-CoV-2 infection with chloroquine or hydroxychloroquine was supposed to be effective at the beginning of the pandemic in Europe, however, it is no longer recommended. Recently hydroxychloroquine has been found unsuccessful in symptom severity reduction and in lowering the risk of disease progression in outpatients with mild COVID-19 [23, 24]. Additionally neither hydroxychloroquine nor chloroquine are not approved by the FDA for the treatment of COVID-19 because of insufficient antiviral effect and serious side effects outweighing the known and potential benefits of these drugs [25]. The list of potential so-far known drugs, that are used in SARSCov-2 infection, is presented in Table 2. Nevertheless, even if the treatment of SARS-CoV-2 infection with chloroquine is thought to be possibly of arrhythmogenic potential, it has been proven only for long time treatment with a high cumulative dose [9].

The presented case showed the arrhythmia as the main manifestation of myocarditis. Due to the receding symptoms of arrhythmia and its mild form in the Holter ECG monitoring, there was no treatment administered. This case aimed to raise awareness of the potential risk of HF development despite the recovery from arrhythmia [1].

The myocardial injury may be irrespective of the severity of the COVID-19 course and airway involvement, regardless of the patient's age, and may also occur in young people. Subclinical cardiac injury may result in the development of HF in further observation. The method of choice for identifying damage is CMR (features of inflammation, oedema, fibrosis, ischemia), other standard diagnostic methods used in cardiology [ECG, echocardopgraphy (ECHO)] allow to document changes in the heart when they are more advanced. CMR occurs to be a method of detecting early and subclinical damage when other methods fail.

Conclusions

The case presented a mild course of myocarditis after SARS-CoV-2 infection in a non-hospitalized 42-year-old patient with no prior history of CV diseases and no burden of CV risk factors with the subsequent development of ventricular arrhythmia.

The pandemic is not coming to the end and the number of patients, including those with complications, continues to grow. While we have no control over non-hospitalized patients, the increased burden of cardiac complication including myocarditis should be considered in future research. Thus, long-term observation is worth to be applied for non-hospitalized COVID-19 survivors.

Conflict of interest

The authors declared no conflict of interest.

Streszczenie

Wśród powikłań choroby koronawirusowej (COVID-19) u hospitalizowanych pacjentów wymienia się między innymi powikłania sercowe. Jednak dane dotyczące powikłań w populacji niehospitalizowanych ozdrowieńców po COVID-19 są nieliczne. W niniejszej pracy przedstawiono przypadek 42-letniej kobiety bez chorób współistniejących, u której 16 marca 2020 doszło do zakażenia SARS-CoV-2 (*severe acute respiratory syndrome-related coronavirus 2*). Pacjentka zgłaszała gorączkę (38°C) i duszność, które ustąpiły po podaniu chlorochiny, bez konieczności hospitalizacji. Tydzień później pojawiło się uczucie kołatania serca i zmęczenie w II klasie czynnościowej według skali *New York Heart Association*. Wyniki kolejnych testów metodą reakcji łańcuchowej polimerazy (PCR) (23 marca, 1 kwietnia) były ujemne. Po 6 tygodniach pacjentka została przyjęta do kardiologa. Wyniki badań laboratoryjnych wykazały nieznaczny wzrost stężeń sercowej troponiny T oznaczonej metodą wysokoczułą oraz N-końcowego fragmentu propetydu natriuretycznego typu B. W elektrokardiogramie (EKG) zaobserwowano pojedyncze ekstrasystolie komorowe o kształcie bloku prawej odnogi pęczka Hisa. W 24-godzinnym zapisie EKG metodą Holtera stwierdzono ponadto objawowe okresy bigeminii i 4,2 tys. ekstrasystolii komorowych. Rezonans magnetyczny serca uwidocznił typowe pozapalne zmiany w mięśniu sercowym bez cech aktywnego zapalenia. U pacjentki nie stosowano farmakoterapii. Objawy ustąpiły, a kontrolny 24-godzinny zapis EKG metodą Holtera w 4. miesiącu po infekcji wykazał ustanie arytmii. Przedstawiony przypadek ukazuje potrzebę rozważenia długoterminowej obserwacji medycznej pacjentów niehospitalizowanych, nawet po łagodnym przebiegu zakażenia SARS-CoV-2.

Słowa kluczowe: infekcja SARS-CoV-2, arytmia, zapalenie mięśnia sercowego, niehospitalizowany ozdrowieniec

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