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Zapalenie mięśnia sercowego w dobie pandemii COVID-19 ze szczególnym uwzględnieniem ludzi starszych – przegląd piśmiennictwa

Myocarditis in the COVID-19 pandemic era with particular attention to the elderly – the literature review

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Streszczenie

Myocarditis to termin medyczny odnoszący się do zapalenia komórek mięśnia sercowego. Mimo, że najczęściej jest następstwem infekcji górnych dróg oddechowych, obecnie, w dobie pandemii COVID-19, pojawiające się dane wskazują na jego coraz większą częstość występowania w związku z tą jednostką. Konsekwencje rozprzestrzeniania się wirusa SARS-CoV-2 są odczuwane bowiem nieustannie na całym świecie. Chociaż choroba dotyczy zwyczaj układu oddechowego, ostra infekcja COVID-19 może objawiać się również zapaleniem kardiomiocytów. Przypadki takie opisywane są również w przebiegu nowej jednostki chorobowej zwanej ‚long COVID syndrome', obejmującej utrzymujące się objawy tygodniami po zakończonej infekcji COVID-19. Kazuistycznie, *myocarditis* może wystąpić po szczepieniu przeciwko SARS-CoV-2. Niniejsza praca ma na celu prezentację zapalenia mięśnia sercowego w dobie pandemii COVID-19, precyzując - w przebiegu ostrej infekcji, jej powikłań w postaci ‚long COVID syndrome' oraz w okresie poszczepiennym, ze szczególnym uwzględnieniem ludzi starszych. Omówiono występowanie, patofizjologię, obraz kliniczny, etapy diagnostyczne i postępowanie. *Geriatria 2022;16:163-170. doi: 10.53139/G.20221622*

Słowa kluczowe: COVID-19, zapalenie mięśnia sercowego, ludzie starsi

Abstract

Myocarditis is a medical term referring to inflammation of cardiac muscle cells. Despite the fact that the most frequently it follows upper respiratory tract infections, emerging data show its increasing prevalence nowadays, in the COVID-19 pandemic era. The consequences of the outbreak of SARS-CoV-2 are being faced until now worldwide. Although the disease most commonly affects the pulmonary system, acute infection can present with myocarditis. Likewise, a new clinical entity called ‚long COVID syndrome', involving the persisting symptoms weeks after the disease is gone, compromises cardiac inflammation. Casuistically, it may appear as a sequela in the post-vaccination period. This review aims to describe myocarditis following COVID-19 disease, long COVID syndrome, and as a post-vaccination against the SARS-CoV-2 complication, with particular attention to the elderly. Prevalence, pathophysiology, clinical presentation, diagnostic steps, and management are discussed. *Geriatria 2022;16:163-170. doi: 10.53139/G.20221622*

Keywords: COVID-19, myocarditis, elderly

Introduction

Myocarditis is a medical term for focal or global inflammation of the heart's muscle cells leading to its damage and loss of function. Subsequently, heart failure, cardiomyopathy, or sudden cardiac death (SCD) can occur. It may have numerous causes, but most frequently it is associated with viral infections, which always have had a significant impact on society worldwide. Cardiotropic pathogens actively destruct cardiomyocytes and cause an acute systemic inflammatory response.

Since the outbreak of SARS-CoV-2 in 2019, the pandemic consequences are being suffered until now. Although COVID-19 usually presents with a respi-

ratory tract infection, most commonly pneumonia, emerging evidence shows the increasing incidence of myocarditis in the disease course. [1,2] It may complicate the hospitalization period leading to high mortality rates, poor outcomes, and further long--term effects. [3] The clinical presentation is highly heterogenous, ranging from a non-symptomatic to a severe, life-threatening condition, which may require mechanical circulation support and if left untreated, may be fatal. [1]

Currently, there is a new clinical entity called „post-COVID syndrome" or „long COVID" or „Post-Acute Sequelae of SARS CoV-2 infection (PASC)" described. It includes various symptoms persisting weeks after the infection is gone, not only within the respiratory system. Myocarditis is reported to be one of the rare post-COVID cardiovascular long-term complications. [4]

Occasionally, cases of myocarditis following vaccination against SARS-CoV-2 were reported. [5]

In this review, we describe myocarditis in the COVID-19 pandemic era in the population of the elderly, providing information on the disease prevalence, clinical presentation, diagnosis, and possible therapeutic options in both acute COVID-19 infection and the following long COVID syndrome. The implication of vaccination is also discussed.

Methods

In this review, PubMed search for the databases, literature, and clinical trials was done. We included papers published in English from 2020 to 2022. Keywords were „myocarditis", „elderly" combined with „COVID-19", „long COVID syndrome", „post-COVID", „COVID vaccine", and „SARS-CoV-2 vaccine". Mostly case reports and case series were found.

Myocarditis in acute COVID-19 disease

Cardiac complications during the acute COVID-19 disease results to be a significant burden [3] and myocarditis is being increasingly reported. [1,2] The exact prevalence is difficult to establish, as most studies describe cardiac injury, which is defined as an elevation of cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (URL), and the term compromises not only myocarditis but also cardiogenic shock, acute coronary syndrome, myocardial infarction, heart failure, arrhythmias, etc. In the recent systematic review summarizing the cardiovascular involvement in COVID-19, the incidence of new cardiac injury was estimated at 7.2-77% and the patients had significantly worse outcomes concerning mortality than the patients without cardiac injury. [3] One retrospective cross-sectional study from Wuhan, China, enrolling 112 patients with a median age of 65, described the evidence of myocarditis at 12.5%. [1] The incidence was higher in the elderly and was associated with a worse prognosis. [1,2] A systematic review of the COVID-19-related myocarditis by S.S.Rathore et al. involving data from 41 studies indicates a higher prevalence in men (71.4% of the patients). The median age was estimated at 43.4 years. [6] In a retrospective cohort study of 1,452,773 patients who tested positive for COVID-19, 4,339 were diagnosed with myocarditis (0.01%). The highest prevalence was noted in adults aged ≥75 years old. Moreover, seasonal peaks were observed. Peaks of the condition were reported in the period of April-May 2020 and November 2020-January 2021. In 2020 the incidence was 42.3% higher than in 2019. [7]

Numerous mechanisms have been proposed to explain the background of COVID-19 myocarditis. Cardiac magnetic resonance (CMR) imaging findings, endomyocardial biopsy (EMB), and COVID-19 sufferers' autopsies result beneficial for understanding the pathophysiology. [8,9,10] The major role is attributed to direct viral damage to the cardiac cells. In the myocardium, like in the pneumocytes, on the cell surface, there is a high expression of angiotensin-converting enzyme 2 (ACE2) receptor, which allows the virus to enter the cells in the way of endocytosis and, subsequently, causes a direct impairment and loss of function. However, in the EMB the presence of SARS-CoV-2 in the cardiomyocytes was reported casuistically. [8] Concerning that, a hypothesis of viral replication and dissemination through the hematological or lymphatic pathway from the pulmonary system was suggested. Microscope images reveal macrophage inflammatory infiltrates and occasionally myocyte necrosis. [8] In an international multicentre study, cardiac tissue was obtained from the autopsies of 21 COVID-19 patients. Increased interstitial macrophages in a majority of the cases were found. Less frequently multifocal lymphocytic myocarditis and other forms of myocarditis were described. [9] A postmortem morphological heart examination of 5 elderly patients (74.8±4.4 years) revealed myocardial infiltrate and combined inflammatory damage of the endocardium. The findings were

consistent with the diagnosis of lymphocytic myocarditis concerning Dallas criteria. [11] Regarding that, systemic inflammation has a crucial role. SARS-CoV-2 triggers the immune response, causes cytokine storm with significant immune system deregulation and provokes a hyper-inflammatory state causing myocardial damage. Consequently, increased levels of interleukin (IL) -6,10, tumor necrosis factor (TNF) can be observed.

Other hypotheses suggest the effect of systemic hypoxemia on the cardiomyocytes. Due to COVID-19-associated pneumonia, there is a decreased energy and oxygen supply to the cardiac cells, which alternate the metabolism from aerobic to anaerobic. As a consequence intracellular acidosis occurs and reactive oxygen species (ROS) are released, causing damage to the DNA molecules and proteins. On the other hand, hypoxia induces an influx of calcium ions leading to apoptosis of cardiomyocytes. Further on, focal or global cardiac inflammation and ventricular dysfunction are observed.

Diagnosing of acute COVID-19-related myocarditis

Clinical presentation varies among patients. [1] The reports of COVID-19 myocarditis in the elderly include cases of a mild-course disease, as well as a fulminant, life-threatening condition. [1,12,13] Symptoms, most commonly, include fever (in the meta-analysis estimated prevalence was 57%), cough, chest pain, dyspnea, or fatigue. [1,6] Occasionally, in more severe cases, patients develop acute heart failure symptoms, cardiogenic shock, or malignant arrhythmias. [12,13] A case of Tako-Tsubo syndrome presenting with myocarditis was also reported. [14]

CMR imaging results to be the most useful and specific diagnostic tool in COVID-19-related myocarditis. It provides detailed information about the exact morphology, pathophysiology, and extent of cardiomyocyte injury. In a recent systematic review of CMR findings in COVID-19 patients, including 24 studies with 199 patients in total, the CMR image was normal in 21% of the individuals. 40.2% were diagnosed with myocarditis. [10] T1 and T2 mapping abnormalities, interstitial edema, and late gadolinium enhancement (LGE) were the most common findings. Perfusion deficits, extracellular volume mapping abnormalities, pericardial effusion, and pericardial LGE were also seen. In the majority, ventricular functions were within normal limits. Given that cardiovascular involvement is linked to an unfavorable prognosis, its detection is crucial and CMR, providing the physician with functional information and tissue characterization, seems significantly beneficial in the differential diagnosis and management strategy.

Among other findings in COVID-19-related myocarditis, *c*Tn and brain natriuretic peptide (BNP) levels were elevated in almost 90% and 87% of the patients, respectively. [6] *c*Tn levels were associated with higher mortality.[1] Noteworthy, troponin levels might have risen before hospital admission due to systemic diseases. Many patients, especially the elderly, suffer from antecedent cardiovascular diseases (CVD) which result in the *c*Tn elevation.

Electrocardiographic (ECG) changes were not pathognomic and included non-specific ST-segment and T-wave changes. [1,6] Sometimes ventricular tachycardia was described. [2] Many kinds of arrhythmias, both bradyarrhythmias and tachyarrhythmias, are commonly seen in myocarditis at any stage of the disease - either ongoing or previous, not only in COVID-19 disease. This may occur due to the electrical instability of the dysfunctional myocardium. Arrhythmic myocarditis due to its heterogeneity and complexity of the clinical presentation, specific diagnostic, prognostic, and therapeutic considerations remains underdiagnosed, complicates the disease's course, and burdens the rapid convalescence.

The transthoracic echocardiography (TTE) imaging most commonly did not unveil any morphological or functional abnormality. [6]

Treatment of acute COVID-19-related myocarditis

Therapeutic options for myocarditis in COVID-19 disease are limited. To date little is known, as there is a paucity of specific, standardized guidance and high-quality, explicit clinical trials concerning the timing, dosage, and duration of any medication. Treatment strategy depends on the clinical course of the disease. Fulminant myocarditis can be managed with glucocorticoids (methylprednisolone, hydrocortisone, prednisolone) or immunosuppressive drugs (interferon α-1b) acting as anti-inflammatories. [12] Also, the use of high-dose intravenous immunoglobulin (IVIG) can be considered. Its function is dual- first, antiviral, and second, anti-inflammatory. IVIG modulates the immune and inflammatory response and has no major side effects. To a certain extent, they may inhibit the

virus replication but their use in the early phase of the disease is required. [12,15] A statement from the ESC Working Group on myocarditis allows the application of glucocorticoids and IVIGs in selected groups of patients, particularly when a viral or autoimmune origin with the presence of autoantibodies is suspected. [16] However, immunosuppression, especially while viral replication is ongoing, may increase the likelihood of more serious clinical illness. Therefore it should be applied with a cautious clinical assessment.

Viral myocarditis should be treated with specific antiviral therapy, but, to date, in SARS-CoV-2-related myocarditis, there is a paucity of officially approved drugs. In the reported cases patients were treated with hydroxychloroquine, azithromycin, colchicine, lopinavir/ritonavir, tocilizumab, oseltamivir, and the symptom relapse was seen. [12,15,17] Additionally, co--existing conditions, like heart failure or arrhythmias, were treated separately according to current, specific guidelines.

Myocarditis as a cardiovascular sequela in long COVID syndrome

There is a new clinical entity described as „post-COVID syndrome" or „long COVID" or „Post-Acute Sequelae of SARS CoV-2 infection (PASC)". It includes various persistent symptoms after the convalescence of acute COVID-19 disease and may present with complications in any human body system, i.e. nervous, pulmonary, renal, immune. The exact mechanism is still to be investigated, but scientists suggest the role of cytokine storm, systemic inflammation, and persistent organ damage. Most commonly patients experience fatigue and general systemic symptoms. [4]

Although cardiac complications are numerously reported in acute COVID-19 infection[1,2,3], as mentioned above, only a few studies were conducted to understand the cardiovascular sequelae in long COVID syndrome, and the reports of myocarditis in PASC are scarce. [4,18] One retrospective analysis reports the increased risk of new-onset myocarditis, in both vaccinated and non-vaccinated patients, in the post-COVID period with a hazard ratio (HR) of 5.38. [4] In a retrospective study of 124 elderly COVID-19 patients, 32 had cardiovascular complications (26%), and 2% were diagnosed with myocarditis. A lower incidence rate and a less complicated course were observed than in the acute period studies. All of the cases occurred in COVID-19 survivors primarily hospitalized in the intensive care unit (ICU). Some cases were complicated with pericardial effusion and inflammation, one progressed to atrial fibrillation. [18] A retrospective study of sixteen patients (median age 68 years) revealed that at ≥2 weeks post-discharge, 69% of patients were asymptomatic. The rest of the individuals experienced persistent cough, dyspnea, or chest pain. [19] However, further investigation is required, as little is known, and the exact prevalence, mechanism, and diagnosis remain a future direction.

CMR findings in long COVID syndrome-associated myocarditis

CMR emerges to be highly effective in diagnosing not only the active COVID-19- associated myocarditis but also the one in long COVID syndrome. [20,21,22] In the systematic review the pooled prevalence of one or more abnormal CMR findings in recovered COVID-19 patients was 46.4% and the pooled prevalence of myocarditis and LGE was 14.0% and 20.5%, respectively. Noteworthy, the incidence of anomalous CMR results was lower in patients with normal cardiac enzyme levels than in individuals with unknown cardiac enzyme levels. [20] In one prospective observational cohort study of 100 COVID-19 survivors in Germany CMR revealed heart involvement in 78% of patients. 60% of the individuals had ongoing myocardial inflammation regardless of any other conditions. [22] In another study, CMR was performed in sixteen patients (median age 68 years) at a median of 56 days post-recovery. the Lake Louise criteria for myocarditis were met in 19% of patients, as they had nonischemic LGE with elevated global T2-mapping values. [23] A cross-sectional study on healthcare workers, with a median age of 52 years, revealed a 26% incidence of myocarditis. CMR abnormalities were seen in 75%. 42% of the patients complained about chest pain, dyspnea, or palpitations, ECG changes were observed in 50%, and the cTn level was elevated just in one patient (1%). [24] Based on that it can be concluded that even despite the absence of any symptoms or left ventricular dysfunction signs, long haulers can suffer from myocarditis. On the other hand, the CMR changes, even if severe, can withdraw spontaneously. A follow-up CMR in COVID-19 survivors revealed resolved myocardial edema in 3 young patients (100%). In one case, a decrease in left ventricular wall thickness and LVEF improvement were observed.[21]

Some authors suggest the potential role of cardiac positron emission tomography (PET) in diagnosing

and assessment of post-COVID-19 myocarditis. In a Turkish cross-sectional study investigating cardiac involvement in COVID-19 survivors, the performed CMR did not reveal any abnormalities in any of the patients, but fluorodeoxyglucose (18F-FGD)-PET imaging showed increased regional 18F-FGD uptake on jeopardized heart segments. Moreover, the NT-proBNP levels were raised. [25] The study proves that patients with myocarditis in long-COVID syndrome may have subtle inflammatory changes available to detect only in high-sensitive PET imaging. It provides supplementary information to CMR and should be considered while myocarditis is suspected.

However, the available data highlight the need for further investigations of cardiovascular sequelae in long COVID syndrome, especially in the elderly. The available evidence is scarce and more studies should be conducted for a better understanding of long COVID-associated myocarditis in the geriatric population.

Role of GLS in diagnosing long COVID syndrome-associated myocarditis

Although CMR is the current gold standard for evaluation of the cardiac structure and function and diagnosing myocarditis, it may not always be performed due to high expense and the need for contrast administration. Recent reports highlight the benefits of the use of global longitudinal strain (GLS) measured by 2D-speckle tracking echocardiography, as it is characterized by a higher sensitivity than the LVEF in identifying myocardial dysfunction at a global and regional level. [26,27] As already mentioned, reports did not show a decrease in LVEF assessed in TTE in the acute COVID-19 infection-related myocarditis, unless the condition was severe. [12] GLS measurement, instead, results beneficial in the identification of subclinical myocardial dysfunction and allows for the early detection of suspected myocarditis, before the LVEF reduction occurs. [26,27,28] A prospective cross-sectional study investigated myocardial dysfunction in COVID-19 elderly patients (median age 62) detected by GLS measurement. The reduction was observed in about 83% of the patients and was more common in critically sick individuals. [28] In a retrospective single-center analysis of the COVID-19 patients (mean age = 66 ± 18) abnormal GLS was found in 80%, and LVEF was preserved (≥50%) in 78%. [26] Another observational cohort study of 18 elderly COVID-19 patients (median age 64 ± 19) showed an increased prevalence of myocardial injury - in most of the patients abnormal GLS in more than one cardiac segment (71% with normal LVEF was recorded. [28] According to data, the GLS findings abnormalities in COVID-19 patients involve the basal segments of the left ventricle (LV). [2,3] Such pattern is not typically observed in other myocarditis and it was described as a „reverse tako-tsubo" morphology. [27] Concerning the above, GLS seems highly sensitive for myocardial dysfunction detection and may be valuable for recognizing myocarditis associated with long COVID syndrome. It can contribute to risk stratification and management strategies. However, to learn more about the prevalence of cardiac involvement in COVID-19 patients, its risk factors, and long-term prognosis, more research is required.

Myocarditis after vaccination against SARS-CoV-2

Vaccine-associated myocarditis prevalence is scarce and not precisely estimated. Most commonly it was associated with smallpox, influenza, or hepatitis B vaccine, and casuistically with other agents. With the emergence of the COVID-19 vaccine emerged the hope for the end of the pandemic. For now, four approved vaccines are available in Europe. Two of them are messenger RNA (mRNA)-based (Pfizer-BioNTech COVID-19 (BNT162b2; Pfizer, Inc; Philadelphia, PA) and Moderna (mRNA-1273; ModernaTX, Inc; Cambridge, MA), while the other two are viral vector (adenovirus)-based (Janssen (Ad.26.COV2.S; Johnson and Johnson; New Brunswick, NJ) and Vaxzevira (previously COVID-19 vaccine AstraZeneca, ChAdOx1 nCoV-19 vaccine, Oxford). In clinical trials, each one of four of them was proven with safety and clinical efficacy. However, despite the fact that adverse effects regarding myocarditis were not seen during any of the coronavirus disease 2019 (COVID-19) vaccine trials, there are reports of myocardial inflammation following vaccination against SARS-CoV-2. [29,30,31]

A recent statement by the Centers for Disease Control and Prevention concludes that some vaccines, notably mRNA vaccines, may have an adverse effect presenting as myocarditis. [32] There is an association between the COVID-19 mRNA vaccines and myocardial inflammation, noted especially in younger males (with a median age of 24) within a few days (median of 3 days) after the second dose. The incidence is estimated at 4.8 cases per 1 million and is higher than

expected in all age groups and in both males and females. The most reported cases were within younger ages. [32] Concerning the findings, the Food and Drug Administration (FDA) added warning information on both mRNA vaccine characterization labels informing of the rare risk of myocarditis. [33]

The exact mechanism of the condition remains unknown. Some RNA molecules, included in the vaccine, may be immunogenic and provoke a cytokine storm, resulting in a systemic high-inflammatory status and, as a part of it, provoking myocarditis. On the other hand, a hypothesis considering a molecular mimicry phenomenon was proposed. Antibodies against spike protein of SARS-CoV-2 may cross-react with structurally similar human proteins and, subsequently, lead to organ deregulation, inflammation, and loss of function. Nevertheless, the area needs more investigations in the future, as cardiac biopsy is not routinely performed, which complicates the highly detailed pathophysiological study.

Regarding post-vaccination myocarditis in the elderly, there is a paucity of explicit evidence and more investigations are required. In one prospective cohort study conducted in England between 1 December 2020 and 24 August 2021, enrolling 28,615,491 patients aged 16 or older vaccinated for COVID-19, 0.004% of them were admitted to the hospital with the diagnosis of myocarditis and 0.001% of the cases occurred after 1-28 after any dose of the vaccine. [29] Increased risk of cardiac inflammation was found with the first dose of CHAdOx1 and BNT162b2 vaccines and both doses of mRNA-1273 vaccine over the 1–28 days post-vaccination period. The incidence risk ratio (IRR) of myocarditis was increased at 1-7 days following the first dose of ChAdOx1 (IRR 1.76), BNT162b2 (IRR 1.45), and mRNA-1273 (IRR 8.38), and the second dose of BNT162b2 (IRR 1.75) and mRNA-1273 (IRR 23.10). As observed, the risk was higher with mRNA-1273 in both doses.

A retrospective cross-sectional study was conducted in forty hospitals in the United States of America (USA) - in Washington, Oregon, Montana, and Los Angeles County, California. Among individuals vaccinated with at least 1 dose of BNT162b2, mRNA-1273, or Ad26.COV2.S vaccine until 25 May 2021, at the median age of 57, twenty had vaccine-related myocarditis (1.0 per 100 000)- four patients following the first dose, sixteen following the second. Nine of them required hospital admission and were discharged after a median of 2 days, without readmission. Myocarditis occurred after a median of 3.5 days following the vaccination. [30]

Another retrospective cross-sectional study in the USA among vaccinated with mRNA vaccine patients revealed 7 individuals with the diagnosis of myocarditis. Four of them were reported with the diagnosis five days after the vaccination. The individuals were three young men and one elderly woman aged 70. Each patient had a history of severe chest pain, and myocardial damage as indicated by the laboratory biomarkers, and required hospitalization. [31]

Bozkurt et al. provided a thorough report on the case reports and case series of myocarditis after COVID-19 vaccination. [5] Most of the studies reported young males after the second dose of mRNA COVID-19 vaccines. All had elevated cTn and the CMR revealed abnormalities. Although the majority required hospitalization, the symptoms withdrew with or without treatment.

Concluding, to date, reports of myocarditis following the vaccination are scarce and further research is required, especially in older adults. However, the risk-to-benefit profile is undoubtedly favorable. COVID-19 vaccines are highly effective in decreasing morbidity and mortality rates, alleviating disease course, and preventing long-term complications. Most reported post-vaccination reactions were mild and did not require any intervention. Older adults are especially predisposed to develop a severe infection course and experience further consequences, so it is necessary to provide them with the vaccine. Nonetheless, a differential diagnosis of any patient complaining about chest pain a few days after the vaccine should include myocarditis.

Conclusions

COVID-19 disease, like other viral infections, has a significant impact on society worldwide. Even though primarily it was associated with respiratory tract involvement, increasing evidence of COVID-19 myocarditis is observed in both the acute phase of the disease and long COVID syndrome, a medical entity including persistent symptoms weeks after the acute phase is gone. Older people with their comorbidities are highly predisposed to develop severe infection and further cardiovascular complications.

The diagnosis of COVID-associated myocarditis is challenging due to disease heterogeneity in clinical

presentation and the lack of specific studies confirming the diagnosis. CMR is reported to be the most specific tool for myocarditis diagnosis, as it provides the clinician with the exact morphological and pathophysiological image.

Despite the fact that the individual cases of cardiac inflammation following vaccination against SARS-CoV-2 were described, the risk-to-benefit profile is favorable and vaccination seems the only possibility to avoid a severe infection course and decrease the post-COVID sequelae incidence, notably in the geriatric population, which is the most predisposed to have a poor outcome.

Notwithstanding, current data reporting myocarditis in the elderly is scarce. Further research is required to establish uniform guidance on the screening, diagnosing, and treatment procedures aiming to prevent post-COVID complications.

Conflict of interest
None

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