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Myocarditis in COVID-19 Patients: A Cross-Sectional Study

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Abstract

Myocarditis is an inflammatory disease of the myocardium, the clinical presentation can vary from an asymptomatic form to dilated cardiomyopathy and heart failure that can be fatal. The gold standard for diagnosis is endomyocardial biopsy, but this is rarely used, leaving for cardiac MRI a wider indication. All this explains the diagnostic difficulty, which is based on a number of arguments. Myocarditis is due to infectious etiologies, essentially viral, but also autoimmune and toxic causes. The SARS-CoV-2 declared responsible for a pandemic in March 2020 is one of the viruses recently implicated in the occurrence of myocarditis. Our study gathered 116 covid-positive patients in order to describe the population having developed myocarditis and to compare these characteristics to the general population.

Keywords: Covid 19; Myocarditis; SARS-CoV-2

Introduction

Myocarditis is an inflammatory condition of the heart muscle that can be identified by histological, immunological, and immunohistochemical criteria. The most frequent cause of myocarditis, particularly in Western nations, is viral infections. The diagnosis is particularly difficult due to the broad spectrum of clinical symptoms, which vary from asymptomatic forms to sudden cardiac death. The gold standard for diagnosis is endomyocardial biopsy (EMB), although this procedure is underutilized in clinical practice. As a result, the diagnosis is frequently made using a combination of clinical presentation, non-invasive biomarkers, and imaging findings [1]. Cardiac magnetic resonance imaging (MRI) is now essential for the diagnosis because it can identify interstitial edema during acute inflammation. Myocarditis has been reported as a possible clinical presentation or complication in patients with coronavirus disease (COVID)-19 due to SARS-CoV-2, which was declared a pandemic by the World Health Organization in March 2020 [2]. This succinct study aims to update and synthesize current understanding of myocarditis in COVID-19 patients and to compare our results with literature.

Patients and Methods

Our work was a descriptive cross-sectional study based on the exploitation of files from the month 04/2020 to the month 02/2022 at the cardiac MRI unit at the National Institute of Oncology of Rabat. Patients with covid involvement retained on clinical, radiological or biological arguments, meeting the definition of covid 19 case of the Ministry of Health [3] of the study period, who have been referred by their attending physician for further exploration by cardiac MRI were included.

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Inclusion Criteria

Patients presenting a symptomatology of covid involvement with a chest CT scan suggesting a high probability of covid-related parenchymal involvement (corads 3 to 5 classification) or with positive PCR with or without cardiovascular symptoms.

Non-Inclusion Criteria

Covid-positive patients with myocarditis symptomatology explained by another cause.

Data Collection and Statistical Analysis

We set up an operating record informing the following data: socio-demographic, clinical, electrical, biological and radiological. The studied variables were reported on the Jamovi software [4]. The quantitative variable age was described in median and interquartile range then compared by non-parametric test of Mann Whitney. The normality of its distribution was decided on the basis of a Shapirowilk test. The qualitative variables were described in numbers and percentages and then compared by chi-square or Fisher exact tests according to the conditions of application of each test. The significance level was set at $p< 0.05$. To determine the associated factors, we performed a binary logistic regression in multivariate analysis. The confidence interval of prevalence was estimated by ESCI Jamovi package.

Ethics Conditions

The ethics committee was not used because this was a retrospective study; data were collected anonymously from the cardiac MRI report registry.

Results

116 patients were included in our study. The prevalence of myocarditis in our study is 32% with 95% confidence interval ranging from 24.1 to 40.8%. There was a predominance of young people who developed post covid myocarditis (median age at 39 years) among them the male sex was predominant at 78,4%. Cardiovascular risk factors were not correlated with the occurrence of myocarditis ($p > 0.05$). None of the myocarditis positive patients were diabetic in the study population, only 8.1% were hypertensive and just 5.4% were followed for dyslipidemia. Chest pain was the primary functional sign found in patients who developed myocarditis; 56.8% with a significance level < 0.05. Dyspnea was found in 13.5% of cases and palpitations in 18.9% of cases who developed myocarditis. The EKG was normal in 22.2% of cases and troponin elevation was found in 88.9%. Left ventricular ejection fraction was preserved in 81.1% of cases with 10.8% having a minimal pericardial effusion (table 1).

Discussion

General updated Knowledge about Viral Myocarditis

Myocarditis is an inflammatory disease of the myocardium caused by different infectious and noninfectious triggers. The exact pathophysiology of myocarditis is not completely understood. We generally distinguish 3 phases: Viral invasion that lasts a few days characterized by lesions resulting from virus replication involving an innate immune response. After that, we describe an autoimmune phase lasting a few weeks to months with activation of the acquired, humoral and cellular immune response. And the late phase is the resolution of myocarditis defining asymptomatic forms, but some patients are unable to eliminate the virus leading to a clinical form of dilated cardiomyopathy. Due to the variety of clinical manifestations, myocarditis diagnosis is frequently difficult. It is challenging to determine the true prevalence

Table 1: descriptive study and univariate analysis.

Variables	Total (n=116)	Myocarditis (yes) n=37	Myocarditis (no) n=79	P value
Age (years)	41,3 ± 16,8	39,3 ± 15,6	42,2 ± 17,4	0,3
Male	81 (69,8)	29 (25)	52 (44,8)	0,1
Female	35 (30,2)	8 (6,9)	27 (23,3)	0,1
Diabetes	5 (4,3)	0	5 (6,3)	0,1
HTA	8 (7)	3 (8,1)	5 (6,4)	0,7
Dyslipidemia	5 (4,3)	2 (5,4)	3 (3,8)	0,6
Chest pain	40 (34,5)	21 (56,8)	19 (24,1)	< 0,001
Dyspnea	9 (7,8)	5 (13,5)	4 (5,1)	0,1
Palpitations	23 (19,8)	7 (18,9)	16 (20,3)	0,8
Normal EKG	5 (17,2)	2 (22,2)	3 (15)	1
Troponin elevation	14 (77,8)	8 (88,9)	6 (66,7)	0,5
Conserved EF	97 (83,6)	30 (81,1)	67 (84,8)	0,5
Presence of PE	20 (17,2)	4 (10,8)	16 (20,3)	0,2

The variable “age” is quantitative and is expressed using: mean value ± standard deviation.
The other variables are qualitative expressed using: effectives (percentage %).

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of myocarditis because endomyocardial biopsy (EMB), the gold standard in diagnosis, is rarely used [5]. A significantly variable autopsy prevalence of myocarditis (2-42%) has been reported in several published investigations [6]. The non-invasive standard reference approach for the diagnosis and monitoring of patients with myocarditis is cardiac magnetic resonance imaging (CMR) [7] which is more affordable and has the particular capacity to directly visualize myocardial necrosis, fibrosis, hyperemia and edema. These items are gathered in The Lake Louise criteria (LLC), first published in 2009. It is about a set of expert consensus recommendations that is frequently used to evaluate MRI findings of myocardial inflammation. In 2018, the LLC were updated to include parametric mapping, which enables quantitative evaluation of local and global myocardial T1 and T2 relaxation times and extracellular volume (ECV) [8]. In comparison to the original LLC, the revised criteria have significantly higher sensitivity (88% vs 73%) while maintaining very high specificity (96%) [9]. Even though the specificity is reduced, the presence of just one marker may nevertheless support the diagnosis of myocardial inflammation in the proper clinical setting. It is important to note that these criteria weren't meant to be used widely as a screening test for myocardial injury in patients with autoimmune diseases. Instead, they were meant to be used in individuals with clinically suspected myocardial inflammation [10]. Even in the midst of little ventricular dysfunction, myocarditis clinical remission frequently occurs spontaneously in patients who first report with minor symptoms. However, biopsy-proven myocarditis can develop into dilated cardiomyopathy (DCM) in up to 30% of cases [1]. In order to track the development of a dilatative phenotype in such circumstances, CMR is useful. An individual patient's prognosis varies depending on the underlying cause. Viral infection is the most frequent cause of myocarditis in developed nations [11]. Additionally, non-viral infections like Borrelia burgdorferi (Lyme disease), Corynebacterium diphtheriae, or Trypanosoma cruzi can cause cardiac inflammation (Chagas disease) [12]. In addition to infectious agents, a number of medications, including antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, and tetracyclines), as well as toxic agents (like drugs used illicitly), can cause hypersensitivity eosinophilic myocarditis, which is typically curable after discontinuing the causative agent [13]. Eosinophilic myocarditis can coexist with autoimmune conditions that have a systemic impact, such as Churg-Strauss syndrome or hypereosinophilic syndrome (Loeffler's illness). Rare causes of inflammatory myocardial illness include sarcoidosis and giant cell myocarditis [5].

Myocarditis in Covid 19 Patients

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) gained worldwide attention at the end of 2019 when it was identified to cause severe respiratory distress syndrome. It was first reported in Wuhan in China and declared a pandemic by the World Health Organization (WHO) in 11 March 2020 [2]. We now have evidence that it affects various organ systems in the human body in addition to the respiratory system, which it principally impacts. Myocarditis, potentially fatal arrhythmias, acute coronary syndrome, systolic heart failure, and cardiogenic shock are a few examples of cardiac symptoms. Myocarditis is becoming more widely recognized as a Coronavirus-19 (COVID-19) consequence and may be caused by either direct viral harm or an exacerbated host immune response. Currently, the precise pathophysiology of myocarditis caused by SARS-CoV-2 is unknown. Proposed mechanisms include immune-mediated, autoimmune-mediated, and direct virus-induced responses, depending on host-related parameters and the stage of infection (acute, subacute, or chronic). There are currently few cases demonstrating pathological proof of direct cardiac invasion by COVID-19 [14]. Sala et al. found coronavirus-like viral particles in interstitial macrophages, but the myocardium did not contain any SARS-CoV-2 genomic material. Xu et al. revealed abnormal postmortem biopsies from a patient who died from COVID-19 in different research. The cardiac tissue showed only a few interstitial mononuclear inflammatory infiltrates and no other significant damage [15].

Prevalence and Socio-Demographic Data

Numerous case reports have described clinical suspicion of myocarditis in patients with coronavirus disease 2019 (COVID- 19), including fulminant forms [16]. If cardiac injury has been reported in 19–28% of patients diagnosed with COVID-19 [17], associated with worse outcomes, the true epidemiology of COVID-19 myocarditis is difficult to establish. Recognizing cardiac involvement is critically important as it portends a significantly elevated risk of in-hospital mortality (51% vs. 4%) and adversely impacts long-term clinical outcomes [17]. Some claimed that myocarditis was responsible for up to 7% of COVID-19-related fatalities [18]. According to one study, 24.5% of COVID-19 patients had coinfections with other viruses [19]. As a result, it's conceivable that many instances of myocarditis linked to COVID-19 were undiagnosed because of SARS-CoV-2. The prevalence of myocarditis in our study is 32% with 95% confidence interval ranging from 24.1 to 40.8%. In our population, there was a predominance of young subjects who developed myocarditis after covid involvement with a mean age of 39.3 years compared to a mean age of 42.2% who did not develop myocarditis, with a male predominance up to 78.4% of cases. Myocarditis is more common in men, with a male/female ratio between 1.5:1 and 1.7:1 [20]. Between December 1st, 2019 and June 30th, 2020, fourteen records were found, totaling fourteen cases that describe myocarditis/myopericarditis thought to have developed as a result of COVID-19 infection [21]. The majority (58% of the cases mentioned) were male, with a median age of 50.4 years. 33 % of all cases involved people under the age of 40. The majority of patients (50%) did not have a known concomitant

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condition, but among those who did, hypertension (33%) was the most common. In our study, cardiovascular risk factors were not correlated with the occurrence of myocarditis. In patients who developed it, the main comorbidity was arterial hypertension in 8% of cases and dyslipidemia in 5.4% of cases. Patients with underlying comorbidities such as cancer, cardiovascular disease, lung disease, diabetes mellitus, obesity, hypertension, etc are more likely to proceed to more serious illness that results in multi-organ failure [22].

Clinical Presentation

The clinical presentation of post-covid myocarditis is highly variable, ranging from asymptomatic forms to life-threatening presentations such as cardiogenic shock or sudden cardiac death associated with ventricular arrhythmias.

In the majority of cases, symptoms related to viral infections are found, namely fatigue, myalgia and respiratory/ gastrointestinal complaints, or more specific covid 19 symptoms as loss of taste or smell, dry cough, sore throat, fever, headache. Sometimes those prodromes are not found and the covid virus attack is directly revealed by cardiac symptoms. The main symptom found in our study population was chest pain, which was found in 56.8% of patients who developed myocarditis after covid infection. Chest pain accounted for 3.4% of presentations in a cohort study from Wuhan, China that included 416 hospitalized patients with confirmed COVID-19 infection [17]. Fulminant myocarditis, which manifests as ventricular dysfunction and heart failure within 2-3 weeks of virus infection, is the most urgent form of the condition [23]. Early indicators of fulminant myocarditis may match those of sepsis, including sinus tachycardia, low pulse pressure, chilly or mottled extremities, and fever.

Complementary Exams Findings

Resting 12-lead EKG and troponin testing may be considered as part of the initial evaluation. Myocarditis may present with electrocardiogram (EKG) abnormalities often associated with pericarditis, such as ST elevation and PR depression, although these findings are not sensitive for diagnosing the condition, and their absence is not conclusive. One myocarditis patient linked to COVID-19, for instance, lacked either PR depression or ST elevation [24]. Other EKG abnormalities that can be seen in myocarditis include bradyarrhythmia with advanced atrioventricular nodal block, new-onset bundle branch block, QT prolongation, pseudoinfarct pattern, or premature ventricular complexes. none of these abnormalities are sensitive or specific enough to establish the diagnosis of myocarditis and are thought to be related to direct myocardial injury caused by SARS-CoV-2, hypoxia, and COVID-19 associated systemic inflammatory response. In some cases, the EKG is normal like in 22% of our patients, which does not rule out myocarditis and requires the support of a set of arguments to make the diagnosis. Numerous cases of severe COVID-19 have been associated with significant blood troponin increase, which may suggest cardiac involvement [25]. According to research by Zhou et al., COVID-19 non survivors had considerably higher high-sensitivity troponin I levels by day 4 (8.8 pg/mL vs. 2.5 pg/mL) than survivors did. In individuals with COVID-19 confirmation, myocardial damage is a predictor of mortality and more serious illness [26]. However, troponin is not specific for the diagnostic of myocarditis and requires other supplementary findings and investigations. Its elevation is mainly associated with a greater risk of developing a severe form of covid infection. Transthoracic echocardiography (TTE) is a very important tool to evaluate the impact of the infection on the myocardium, it also allows the detection of pre-existing heart disease and the elimination of differential diagnoses of myocarditis, namely ischemic heart disease. Point-of-care ultrasonography should be strongly considered as a first screening test for COVID-19 positive or suspected patients, according to the Canadian Society of Echocardiography [27]. TTE observations can include dilated and/or hypertrophic ventricles, localized wall motion abnormalities, and global left ventricular hypokinesis. In a systematic review of MEDLINE and Cochrane Library (1/12/19–30/09/20) where 38 cases were included, out of 34 patients with available echocardiographic data, in seven cases, there was no any structural or functional abnormality [28]. Another study showed that most of the cases (60%) had reduced ejection fraction in those whom TTS was performed (83% of the cases) [21]. In our population, there is a predominance of preserved ejection fraction (81,1%). Pericardial inflammation which can be associated to pericardial effusion may occur in quite varied spectrum of conditions, including viral infections. In our study, 10,8% of positive covid patients who have developed myocardial injury have developed a minimal pericardial effusion. In another study including 26 competitive collegiate athletes from Ohio with confirmed COVID-19, two athletes with CMR evidence of myocarditis had coexisting pericardial effusions [29].

Before the COVID-19 pandemic, cardiac magnetic resonance (CMR) imaging was frequently used to diagnose myocarditis, particularly when endomyocardial biopsy (EMB) is not attempted or not possible. Patients who are unstable and have severe cardiac failure, vascular shock, ventricular arrhythmia, or high-grade AV block should get an EMB instead of a CMR. This is the main diagnostic tool used in our study, which allowed us to diagnose myocarditis in patients with covid infection and to deduce the characteristics of the study population.

Conclusion

Our understanding of COVID-19's consequences is expanding rapidly. It has been established that myocardial damage and myocarditis are linked to greater rates of morbidity and mortality. There are still a lot of unanswered concerns and places to investigate despite the fast-

expanding research on the management of COVID-19 and its consequences. Currently, little is known about the management of myocarditis and the majority of ongoing research focuses on the pulmonary problems of COVID-19. It is crucial to be aware of myocarditis as a COVID-19 sequela, and a multidisciplinary team should be established for all COVID-19 patients with clinically suspected myocarditis due to the potential for rapid deterioration in those patients. More research is required to discover and comprehend the connection between myocarditis and this pandemic virus.

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