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Maria Vincenza Polito¹ · Amelia Ravera²¹ Division of Cardiology, Department of Internal Medicine, Evangelic Hospital Betania, Naples, Italy² Department of Cardiology, A.O.U. “San Giovanni di Dio e Ruggi D’Aragona”, Salerno, Italy

Myocarditis in the era of SARS-CoV-2: one piece of a complex puzzle?

To the Editor

We read with great interest the recently published article by Chen et al. [1], which underlines the potential association between fulminant myocarditis (FM) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The authors report that during SARS-CoV-2 infection the clinical picture in some patients may deteriorate rapidly with acute distress syndrome, septic shock, severe multiple organ failure, and FM. Moreover, they point out that SARS-CoV-2-associated FM requires great attention, owing to its high mortality rate ranging from 40 to 70% [2]. Interestingly, in the retrospective analysis by Ruan et al. [3], among 68 fatal SARS-CoV-2 cases, 7% showed myocardial injury (MI) attributed to myocarditis with circulatory failure and, in 33% of cases, myocarditis was considered to have contributed to the outcome.

To date, the true dimension of the problem is unfortunately unknown because many cases of SARS-CoV-2-associated myocarditis are probably not diagnosed; only anecdotal cases are reported in the literature, and there is still very little evidence available on cardiac involvement in SARS-CoV-2 infection. With the increasing number of SARS-CoV-2 cases worldwide, we believe this is a hot topic that warrants urgent discussion.

Firstly, we still do not know whether MI reflects a direct attack by the virus or represents an effect of the cytokine storm in the context of an imbalanced inflammatory response [4]. Some data from autopsy studies [5] suggest there

are no obvious histological changes in heart tissue, except for interstitial infiltration of inflammatory cells. Hence, it is reasonable to hypothesize that the pro-inflammatory systemic state induced by viral infection would lead to MI [6].

Secondly, discordant data are reported about the current incidence of SARS-CoV-2-induced acute MI. In the initial study by Wang et al. [7] of 138 patients, only 7.2% were diagnosed as having MI, documented mainly on the basis of elevated values of high-sensitive troponin I (hs-cTnI) or new ECG or echocardiographic abnormalities. In another case series study [8] that enrolled 187 patients, a higher percentage (27.8%) showed MI, which resulted in an increased incidence of cardiac dysfunction and malignant arrhythmias. It is noteworthy that the mortality was markedly higher in patients with elevated plasma TnT levels than in patients with normal TnT levels (59.6% vs. 8.9%; $p < 0.001$). Furthermore, there was a positive linear correlation between TnT levels and plasma high-sensitivity C-reactive protein levels ($r = 0.281$; $p < 0.001$), and patients with high TnT levels also had higher procalcitonin values, suggesting that MI may be closely associated with an inflammatory state during the course of disease. These findings were confirmed in a larger population of 416 patients [9] where in-hospital mortality, pulmonary and renal complications, higher inflammatory markers, electrolyte disturbances, and coagulation disorders were more common in patients with cardiac injury.

Therefore, the following question is raised: “How should we interpret ele-

vated cardiac biomarkers in the context of SARS-CoV-2 infection?” In the aforementioned studies, we believe that the rate of MI is likely dependent on the definition used and the grade of disease severity in the patients. Especially in critically ill SARS-CoV-2 patients, an increase in cardiac biomarkers may originate from different causes such as pneumonia, renal insufficiency, arrhythmias, ischemia, and myocardial inflammation. Furthermore, in this difficult context, the current studies lack evidence from cardiac magnetic resonance (CMR) or endomyocardial biopsy (EMB) to determine the distribution and the features of MI—which are often reported only on the basis of troponin increases and ECG abnormalities—and to confirm definitely the diagnosis of myocarditis.

Thus, the main problem is to diagnose correctly SARS-CoV-2-associated myocarditis, as suggested by the position statement of the European Society of Cardiology (ESC) Working Group [10], and to consider differential diagnoses in a complete work-up (■ Fig. 1). In the SARS-CoV-2 era, the clinical utility and the role of EMB, currently the gold standard for confirming the diagnosis of myocarditis, remain unclear; furthermore, there is great difficulty in performing noninvasive imaging such as echocardiography and CMR with adequate precautionary and isolation measures.

Another important issue is that in some cases SARS-CoV-2 infection might initially not appear with clear signs and symptoms suggestive of interstitial pneumonia but may appear as myocarditis without respiratory symptoms [11],

Fig. 1 ◀ Virus-induced multiorgan damage and diagnostic work-up for myocardial injury

sometimes complicated by cardiogenic shock with a fulminant course [12].

Current guidelines do not recommend the use of routine viral testing for clinically suspected myocarditis; however, this recommendation should probably be revised, especially in the presence of a high clinical suspicion of SARS-CoV-2 infection in order to guarantee appropriate identification and prompt isolation of infected patients.

In addition, there is poor evidence on the therapeutic management of SARS-CoV-2-associated myocarditis. It has been suggested [12] that early glucocorticoid and immunoglobulin therapy could be beneficial for this type of patient. To date, there is great confusion around the use and the utility of steroids during SARS-CoV-2 infection. Corticosteroids have been used in several viral respiratory infections (influenza, SARS-CoV, and MERS-CoV) demonstrating a limited benefit and, in some cases, delaying viral clearance and increasing mortality [13]. However, the ESC Working Group on Myocardial and Pericardial Diseases [10] indicates the use of steroids in proven autoimmune myocarditis and in virus-negative forms only after ruling active infection on EMB. It is evident that in real practice, EMB is not always available and its role in SARS-CoV-2-related myocarditis is still unknown. Moreover, in the absence of multicenter randomized studies, the

routine use of immunoglobulin is also not recommended.

In conclusion, we believe that there are significant gaps in the assessment of MI in SARS-CoV-2 patients that require a complete diagnostic work-up, prioritized treatments, and even more aggressive strategies [14, 15] if necessary, especially in those developing cardiogenic shock during FM.

Undoubtedly, we still have many unanswered questions and further studies are needed to clarify these important issues.

Corresponding address

Maria Vincenza Polito

Division of Cardiology, Department of Internal Medicine, Evangelic Hospital Betania
Naples, Italy
mvpolito@hotmail.it

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Unterschiede der Immunreaktion gegen SARS-CoV-2 bei milden und schweren COVID-19-Krankheit

Warum erkranken Menschen, die sich mit SARS-CoV-2 infiziert haben, unterschiedlich schwer an der davon ausgelösten Krankheit COVID-19?

Wissenschaftlerinnen und Wissenschaftler um Prof. Dr. Mascha Binder von der Universitätsmedizin Halle (Saale) haben dazu mehr als 14 Millionen Rezeptor-Sequenzen von B- und T-Zellen, also Immunzellen, untersucht, die sie aus Blutproben von COVID-19-Patientinnen und -Patienten gewonnen haben. Die Ergebnisse hat die Gruppe im Fachmagazin „Immunity“ (CellPress) publiziert.

„Das Projekt zeigt Charakteristika von Immunantworten gegen Sars-CoV-2 bei milden und schweren Krankheitsverläufen auf. Die Unterschiede in den Immunantworten legen nahe, dass das Erreichen einer frühen schützenden Immunität oder auch das Verhältnis von schützenden und nicht-schützenden Anteilen in der Immunantwort darüber entscheiden kann, ob eine schnelle Viruseliminierung und Abheilung gelingt und sich ein pathologischer Entzündungszustand und damit schwerer Erkrankungsverlauf vermeiden lässt. Unsere Daten geben somit einen grundlegenden Einblick in die erworbene Immunität gegen SARS-CoV-2“, erklärt Mascha Binder, Professorin für Onkologie und Hämatologie sowie Direktorin der Universitätsklinik und Poliklinik für Innere Medizin IV der Universitätsmedizin Halle (Saale).

Auffällige Laborwerte auch noch Wochen nach der Ausheilung

Erstaunlich sei auch, dass man habe zeigen können, dass viele junge Patientinnen und Patienten mit milden Verläufen und schneller Erholung auch noch Wochen nach der Ausheilung auffällige Laborwerte zeigen. „Neben überschießend regenerierenden Immunzellen finden sich pathologische Muster in kardiovaskulären Risikofaktoren und in Interferonen, das sind bestimmte Botenstoffe, die in der viralen Abwehr eine Rolle spielen, aber auch mit Vermehrung von Bindegewebsfasern und Vernarbung in bestimmten Geweben wie der Lunge einhergehen können“, erklärt die Wissenschaftlerin und Ärztin. Ob dies in dieser Patientengruppe mit einem erhöhten Risiko für Folgeerkrankungen assoziiert sei, müsse mit weiteren Langzeitbeobachtungsstudien geklärt werden.

Die Blutproben waren dabei sowohl von Menschen mit überstandener als auch von Menschen mit aktueller COVID-19-Erkrankung entnommen worden. Als Vergleichsgruppe diente eine altersangepasste Kohorte, die negativ auf COVID-19-Antikörper getestet wurde.

Doch nicht nur die Publikation steht der Wissenschaftswelt und Öffentlichkeit zur Verfügung, sondern auch die identifizierten Immunrezeptorsequenzen werden in einer öffentlichen Datenbank abgelegt. „Sie können damit von der wissenschaftlichen Gemeinschaft genutzt und zum Beispiel für diagnostische Anwendungen, aber auch zur Entwicklung einer passiven Immuntherapie mit neutralisierenden Antikörpern weiterentwickelt werden“, so Binder.

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**Cornelia Fuhrmann,
Martin-Luther-Universität Halle-
Wittenberg**