Case report of severe PCR-confirmed COVID-19 myocarditis in a European patient manifesting in mid January 2020

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Background
Viral genesis is the most common cause of myocarditis. COVID-19-associated myocarditis seems to be a notable extrapulmonary manifestation, which may result in the need for a different treatment. There has been no positive polymerase chain reaction (PCR) testing of SARS-CoV-2 in heart specimens, thus far.

Case summary
A 48-year-old male patient presented with fever, dyspnoea, and haemoptysis. Laboratory findings showed highly elevated inflammatory and cardiac damage markers. Thoracic computed tomography (CT) revealed bilateral, patchy peripheral ground-glass opacities with a crazy-paving pattern, focal consolidations, and mild pleural effusions. Cardiac imaging with echocardiography and magnetic resonance imaging (MRI) detected a reduced biventricular function. MRI additionally showed myocardial oedema and late gadolinium enhancement. Lung and heart biopsies were performed, revealing alveolitis with necrosis and acute lymphocytic myocarditis. Testing for usual cardiotropic viruses was negative, and no aspects of vasculitis or granuloma could be found. Due to fulfilling the criteria, the patient was diagnosed with rheumatic vasculitis. Treatment with cyclophosphamide and steroids was initiated. Later, the patient reported a history of travel to Tyrol in mid January. Consequently, PCR testing for SARS-CoV-2 was performed, which was positive in the heart specimen. Immunosuppressive treatment was discontinued. During a follow-up visit at the end of April, the patient’s recovery was stable.

Discussion
In COVID-19 infections, myocardial inflammation can be present as an extrapulmonary manifestation. Positive PCR testing confirms myocardial invasion of the virus. Imaging and laboratory studies correlate with the histopathological findings, and thus should be performed in COVID-19 patients who are suspicious for myocarditis. Supportive treatment with steroids may be useful in these patients.

Keywords
Myocarditis • COVID-19 • SARS-CoV-2 • Cardiac imaging • Case report

Primary specialties involved: Rheumatology Cardiology Radiology Pathology
Introduction

The outbreak of COVID-19, caused by the novel coronavirus SARS-CoV-2, has affected a huge number of patients worldwide. In the vast majority of cases, this viral infection is characterized by upper respiratory tract and pulmonary manifestations. However, extrapulmonary manifestations of the disease are also increasingly being reported.1–5 Here, we present a case of severe COVID-19 myocarditis manifesting in mid January 2020. This case was primarily suspected of being related to small-vessel vasculitis, but had to be revised to COVID-19-associated disease based on additional polymerase chain reaction (PCR) analysis of the myocardial biopsy.

Timeline

| Date               | Event                                                                 |
|--------------------|-----------------------------------------------------------------------|
| 24 January 2020    | First admission to our hospital with fever, dyspnoea, and haemoptysis. |
| 28 January 2020    | Thoracic CT with biopsy.                                              |
| 29 January 2020    | Cardiac MRI, echocardiography.                                        |
| 31 January 2020    | Myocardial biopsy.                                                    |
| 6 February 2020    | Initiation of immunosuppressive treatment.                            |
| 1 April 2020       | Revisitation of patient’s history; prior vacation in Tyrol and flu-like symptoms of patient’s daughter were reported. |
| 2 April 2020       | PCR testing of myocardial specimen for SARS-CoV-2.                    |
| 4 April 2020       | Positive result of PCR testing is returned.                           |
| 9 April 2020       | Discontinuation of immunosuppressive treatment.                       |
| 30 April 2020      | Follow-up presentation: improved laboratory parameters and cardiac function diameters, cardiac MRI without inflammation. |

Case presentation

On 24 January 2020, a 48-year-old male patient with a history of asthma was transferred to our department due to acute myocarditis of unknown origin. The patient described a sudden onset of high-grade fever without prodromal symptoms beginning on 12 January. Within a few days, he developed dyspnoea and haemoptysis requiring hospital admission.

Laboratory testing showed high levels of the inflammatory markers creatine phosphokinase (CPK) and lactate dehydrogenase (LDH; see Table 1). Ferritin was only marginally elevated. His differential blood count showed prominent eosinophilia (19%) and lymphopenia (18%). Testing for autoantibodies only yielded antinuclear antibodies (ANAs) at a very low titre without any detectable specificity against a broad panel of nuclear antigens. However, myositis-associated antibodies, antineutrophilic cytoplasmic antibodies (ANCA), as well as antiphospholipid antibodies were negative. The measurement of vital signs revealed tachycardia (100 b.p.m.) with hypotonic blood pressure (90/65 mmHg) and fever (39°C). On physical examination, lower leg oedema was present. The auscultation of heart and lungs was unremarkable.

Thoracic computed tomography (CT) showed bilateral, patchy peripheral ground-glass opacities with a crazy-paving pattern, focal consolidations, and mild pleural effusions (Figure 1A). Due to highly elevated cardiac markers [N-terminal probrain natriuretic peptide (NT-proBNP) and troponin T], echocardiography and cardiac magnetic resonance imaging (MRI) were performed. Both showed highly reduced ventricular function [left ventricular ejection fraction (LVEF) 22%, right ventricular ejection fraction (RVEF) 28%]. Furthermore, late gadolinium enhancement (LGE) of the entire left ventricular myocardium with intracardial thrombi was detected on MRI (Figure 1B–K). T1 and T2 times were markedly prolonged, reflecting acute oedema following myocardial inflammation. In light of a multifaceted differential diagnosis, pulmonary and myocardial biopsies were performed. Histopathological analysis of the pulmonary biopsy showed interstitial alveolitis with capillaritis, necrosis, and mild eosinophilia. The cardiac specimen revealed active lymphocytic myocarditis (Figure 2A–D). PCR analysis for usual cardiotropic viruses was negative. A few days after admission, the patient developed an acute renal injury with microhaematuria.

Based on these findings and the clinical presentation at that point, the diagnosis of an ANCA-negative small-vessel vasculitis was established. Given the known asthma, eosinophilia, renal injury with microhaematuria, and cardiopulmonary inflammation, the patient fulfilled the criteria for eosinophilic granulomatosis with polyangiitis (EGPA) despite the lack of ANCA.

In accordance with current guidelines, pulse therapy with cyclophosphamide and high-dose steroids was initiated, and the patient recovered adequately after several weeks of treatment. On discharge, the patient was afebrile without dyspnoea, but a wearable defibrillator was prescribed.

After discharge of the patient from our hospital, the COVID-19 pandemic had evolved to affect Europe as well. Individual cases were reported at the end of January and early February in France, Italy, and Austria. Owing to the initial broad spectrum of differential diagnoses, we revisited the complete medical history and contacted the patient,

Learning points

- Myocarditis is a notable and threatening complication of COVID-19.
- Cardiac imaging should be performed in COVID-19 patients with suspected myocarditis.
- Supportive treatment may include immunosuppressive agents.

Table 1
who reported a prior vacation in Tyrol, Austria, from which the patient and his family had returned 1 day before the sudden onset of his symptoms. It is of interest that Austria is considered the origin of the COVID-19 outbreak in Europe. The distance from Tyrol to our department in Germany is 500 km. One week later, the patient arrived at the hospital because of a progressive fever and weakness. Moreover, the patient reported that his 8-year-old daughter developed flu-like symptoms with a high-grade fever (40.7°C/105°F) 1 week after his first symptoms.

Subsequently, PCR testing for SARS-CoV-2 RNA was initiated on the histological specimens of the heart using quantitative reverse transcription–PCR (RT–qPCR) kits targeting the E gene and RdRp gene (TIB MOLBIOL, Roche Diagnostics, Germany), and the N2 assay (N gene). Unexpectedly, those tests were positive for SARS-

| Parameter                                | Result  | Reference range |
|------------------------------------------|---------|-----------------|
| C-reactive protein (CRP)                 | 13.0 mg/dL | 0–0.5 mg/dL    |
| Leucocytes                               | 13.8/nL | 3.5–10.0/nL    |
| Lymphocytes                              | 18%     | 25–40%         |
| Eosinophils                              | 19%     | 2–4%           |
| Lactate dehydrogenase (LDH)              | 1249 U/L | 135 – 225 U/L  |
| Creatine phosphokinase (CPK)             | 428 U/L | 39–308 U/L     |
| Antineutrophil cytoplasmic antibodies (ANCA) | Negative | Negative |
| Antinuclear antibody (ANA) titre         | 1:160   | <1:80          |
| ANA differentiation                       | Negative | Negative |
| Creatinine                               | 2.1 mg/dL | 0.7–1.2 mg/dL |
| NT-proBNP                                | 12,232 pg/mL | 1–300 pg/mL |
| Troponin T (highly sensitive)            | 3264 pg/ml | 0–14 pg/mL    |
| Soluble interleukin-2 receptor (sIL-2-R) | 1500 U/mL | 223–710 U/mL  |
| Ferritin                                 | 468 ng/mL | 30–400 ng/mL  |

Figure 1 (A) Thoracic CT showing bilateral, patchy peripheral ground-glass opacities with a crazy-paving pattern, focal consolidations, and mild pleural effusions. There is also a large thrombus in the left ventricle (arrow). (B) Cardiac MRI: T1 mapping with a prolonged global native T1 time of 1209 ms (cut-off 1170 ms at 3T). (C) Cardiac MRI: T2 mapping with a prolonged global T2 time of 44 ms (cut-off 41 ms at 3T). (D) Cardiac MRI; phase-sensitive inversion recovery gradient echo imaging (PSIR) showing extensive late gadolinium enhancement (LGE) of the entire left ventricular myocardium; with dark foci probably representing areas of microvascular obstruction (MVO). (E) Cardiac MRI: cine retro sequence with four-chamber view revealing a large thrombus in the left ventricle (arrow). (F) Cardiac MRI: three-chamber view, PSIR. (G) Cardiac MRI: three-chamber view, PSIR, with TI 600 revealing thrombi. (H) Cardiac MRI: four-chamber view, PSIR. (I) Cardiac MRI: basal short axis: PSIR. (J) Cardiac MRI: four-chamber view, PSIR, follow-up, generalized LGE and areas of MVO have resolved; LGE is condensed; (K) Cardiac MRI: basal short axis, LGE, follow-up.
CoV-2 RNA. Therefore, we revised the diagnosis from small-vessel vasculitis to COVID-19-associated myocarditis and immediately stopped immunosuppressive treatment with cyclophosphamide. The steroid dose was also tapered. The course of resolving the intracardial thrombus was accomplished with a therapy that included coumarin-type drugs. The normalization of elevated laboratory inflammation markers, improvement of cardiac function on echocardiography, and the absence of cardiac inflammation on cardiac MRI confirmed the patient’s recovery.

**Histopathological analyses**

The pulmonary specimen showed mild eosinophilia with parenchymal necrosis and alveolitis. Staining for CD31, factor VIII, and CD68 were positive, while all other staining experiments were negative. In the cardiac specimen, markedly elevated counts of lymphocytes (positive for LFA-1, CD45R0, and CD3) and elevated counts of macrophages (positive for MAC-1) could be detected along with the expression of adhesion molecules (ICAM-1). In contrast, perforin-expressing cytotoxic cells were not present. While PCR did not detect typical cardiotropic viruses, additional testing for SARS-CoV-2 RNA revealed a positive signal in the myocardium.

**Discussion**

In this work, we present a case of severe COVID-19 myocarditis confirmed by PCR analysis of a myocardial biopsy specimen. We additionally confirmed potentially lethal organ involvement of an infection with SARS-CoV-2.1

The worldwide COVID-19 pandemic is both a challenge for healthcare, as well as unknown territory with respect to several aspects of SARS-CoV-2-triggered pathophysiology. Apart from the dominant pulmonary symptoms, much less is known about extrapulmonary symptoms and manifestations. In addition to reports on neuronal invasion,2 gastrointestinal manifestation,3 and alteration of...
the lymphocyte profile, myocardial injury and other cardiac manifestations are still an emerging field of knowledge.4,5

With respect to the systemic aspects of a SARS-CoV-2 infection, other systemic inflammatory diseases need to be considered at the time of diagnosis. Among the rheumatic diseases, small-vessel vasculitides in particular present with symptoms similar to COVID-19. EGPA is one of these classical small-vessel vasculitides, which frequently causes systemic organ involvement,6 whereas ANCA positivity is found only in 40–60% of the patients.7

The case presented here highlights this difficulty in times of intensive COVID-19 presence in the admission centres of hospitals. The time at which our patient arrived at the hospital in mid January was at a very early phase in the COVID-19 pandemic. The first confirmed patient in Europe was dated at 24 January,8 and in Germany on 27 January. The diagnosis of EGPA, in addition to sarcoidosis,9 was at that time the most likely, supported by fulfillment of the classification criteria and adequate response to immunosuppressive treatment.

However, due to the clinically atypical profile of the suspected EGPA, particularly the lack of definite proof by pulmonary biopsy, and the markedly elevated cardiac parameters, together with typical MRI signs of myocarditis,10–12 a myocardial biopsy was performed. This was despite a high risk of complications, revealing a histological hint of a potential viral or post-viral myocarditis.12,13 In this situation, eosinophilia might be seen in the context of the formerly known asthmatic disease of the patient.

Based on the histopathological evaluation, the negative molecular results for usual myocarditis-triggering viruses and the emerging COVID-19 pandemic, PCR analysis was performed. This resulted in the detection of SARS-CoV-2 RNA, and this was thus the first documented patient with COVID-19 myocarditis.

Subsequently immunosuppressive therapy5,14 was terminated. However, fortuitously, it may have prevented a catastrophic inflammatory status in the myocardium, as can typically be observed in COVID-19 manifestation of the lungs. Thus far, there are limited data to suggest that use of immunosuppressive agents in COVID-19-associated cardiac involvement may be useful.15 Discontinuation was determined to prevent possible opportunistic infections and because of the lack of autoimmune diagnosis.

Taken together, cardiac involvement in COVID-19 seems to be a notable complication. Cardiac damage can be detected based on laboratory testing, imaging, and histology. We recommend cardiac MRI in the case of laboratory aspects of cardiac damage and sudden onset of cardiac failure confirmed by echocardiography. Serum levels of troponin, NT-proBNP, and creatine phosphokinase can be elevated in myocarditis and point to cardiac involvement in COVID-19. In this case, late gadolinium enhancement images showed dark foci within the extended late gadolinium enhancement, which most probably represent areas of microvascular obstruction, as inflammatory vasculopathy has been shown to be a typical pathophysiological feature of COVID-19.4

In the case presented here, laboratory findings and cardiac imaging are in line with histopathological findings in COVID-19. So far, COVID-19-associated myocarditis has not been proven by PCR from myocardial tissue of deceased patients.16 Recently, histological confirmation of coronavirus particles in endomyocardial specimens via electron microscopy was conducted, showing direct viral invasion of heart tissue.17 In addition to possibly dating Europe’s first confirmed COVID-19 infection from 24 January9 to 12 January, we proved PCR testing of the heart tissue to be an effective way to diagnose COVID-19 in unclear clinical situations.

Lead author biography

Ole Hudowenz was born in Güstrow, Germany in 1990. He attended medical school at Justus-Liebig-University in Giessen. After his first employment at Sana Clinic in Offenbach as a medical doctor he now works as internal resident at the Department of Rheumatology and Immunology at Campus Kerckhoff of Justus-Liebig University in Bad Nauheim. His main interests are rare and systemic diseases.

Supplementary material

Supplementary material is available at European Heart Journal – Case Reports online.

Slide sets: A fully edited slide set detailing this case, suitable for local presentation, is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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