DOI: 10.1111/pin.13184

LETTER TO THE EDITOR

Pathology International WILEY

Post-mortem differential diagnosis from COVID-19: A case of fulminant myocarditis HHV-6 related

To the Editor,

Human herpesvirus 6 (HHV-6), a T-cell lymphotropic virus, is the sixth recognized member belonging to the Herpesviridae family and has been identified as the etiologic agent of exanthem subitum (Zahorsky's disease, sixth disease, and roseola infantum), a common childhood disease.[1] HHV-6 infection can reactivate in immunocompromised or in immunocompetent adults and may cause encephalitis, interstitial pneumonia, and myocarditis with a high mortality rate, especially in fragile patients, although these effects occurred less frequently in immunocompetent hosts.[2] Fulminant myocarditis is an acute inflammation of the myocardium that could manifest itself with unspecific symptoms like fatigue and shortness of breath or chest discomfort. Therefore, the diagnosis and treatment are often delayed with a worse prognosis. Many viruses can cause fulminant myocarditis, including Coxsackievirus B, adenoviruses, parvovirus B19, Epstein–Barr virus (EBV), cytomegalovirus (CMV), HHV 6 and, more recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here, we report a fatal case of HHV-6-related fulminant myocarditis with interstitial pneumonia and necrotizing vasculitis in an immunocompetent adult.

A 59-year-old man was admitted to the hospital for fever and dyspnea for 3 days, resistant to therapy with antibiotic and antipyretic. His medical history showed hypertension and obesity. At admission, the clinical examination revealed: temperature of 37.7°C, heart rate of 115/min, blood pressure of 120/85 mmHg, oxygen saturation 93%, bilateral decreased breath sounds, and lower right leg reddened.

Standard hematologic tests and blood chemistries showed increased levels of c-reactive protein (CRP), white blood cell count of 14 100/μL with neutrophilia, lymphocytopenia, and thrombocytopenia, elevated levels of troponin (115 06 ng/L), transaminase, and bilirubin.

Chest computed tomography showed: parenchymal thickenings with aerial bronchogram localized on the right lung's apex and middle lobe, diffuse and bilateral "ground glass" areas, pleural and pericardial effusions, and lymphadenopathy. That nonspecific clinical picture was compatible with different viral infections, including COVID-19. However, the patient presented two nasopharyngeal swabs negative for SARS-CoV-2.

The following day the fever was down but the oxygen saturation was still lower than normal.

An electrocardiogram showed sinus tachycardia and echocardiogram confirmed the pericardial effusion without signs of cardiac tamponade and revealed an ejection fraction of 60%.

On the third-day blood chemistries confirmed the neutrophilic leucocytosis and showed a further increase of aspartate aminotransferase (133 U/L), alanine aminotransferase (205 U/L), and high D-dimer level (3446 ng/mL). During the same day, the patient suddenly died of cardiac arrest. During the short hospitalization, the patient was treated with antibiotics (clarithromycin, ceftriaxone, and hydroxychloroquine) and heparin.

To determine the cause of death a complete post-mortem examination was performed at the INMI L. Spallanzani-IRCCS Hospital (Rome, Italy). The study was approved by the local ethics committee (Ethics Committee approval number 9/2020).

Whole body post-mortem examination was performed according to guidance for post-mortem and collection and submission of specimens and biosafety practices, to reduce the risk of transmission of infectious pathogens during and after the post-mortem examination. Since SARS-CoV-2 is classified as a BSL3 organism, specific operating procedures for BSL3 pathogens were followed. Autopsies were performed in a specific COVID-19 designated autopsy room with airflow control and airborne infection control procedures including use of appropriated PPE (i.e., NIOSH-certified disposable N-95 respirator).

Macroscopic findings revealed pleural effusion (about 250 and 500 mL respectively on the left and the right) and pericardial (500 mL) reddish-tinted fluids, typically due to blood effusion. Lungs were significantly increased in volume and consistency with diffuse pleural thickening; cut surface showed consolidation of lobes and red congested areas.

Bronchi were dilated and pulmonary vasculature showed no blood clots or local thrombosis. The heart showed increased size and weight (500 g) with

© 2021 Japanese Society of Pathology and John Wiley & Sons Australia, Ltd

concentric left ventricular hypertrophy, increased right and left ventricular wall thickness and mild left atrial dilatation; the endocardium showed punctuate petechial hemorrhages. The coronary arteries and heart valves were unremarkable, except for isolated hypertrophy of the papillary muscles.

The liver was increased in volume and consistency and the parenchyma revealed micronodular formations on the cut surface.

The histopathological examination of the heart revealed active myocarditis (Figure 1a–c) and pericarditis, following Dallas criteria, characterized by lymphocytes, macrophages, and eosinophils granulocytes associated with large clusters of myocytes necrosis and myofibers disarray (Figure 1d). Wavy and hypertrophic myofibers were observed in a contest of myocardiosclerosis. Even in the heart tissue, there was diffuse necrotizing vasculitis with an inflammatory infiltrate formed by lymphocytes, monocytes, and eosinophils granulocytes (Figure 1e). The coronary arteries were patent but presented fibrous hyperplasia and an inflammatory infiltrate of the intima and media layers (Figure 1f).

Histologic sections of the lungs demonstrated diffuse interstitial lymphocytic inflammation (Figure S1a,b), necrotizing vasculitis with an inflammatory infiltrate in the layers of the small and medium-sized vessels consisted of lymphocytes, neutrophils and a significant number of

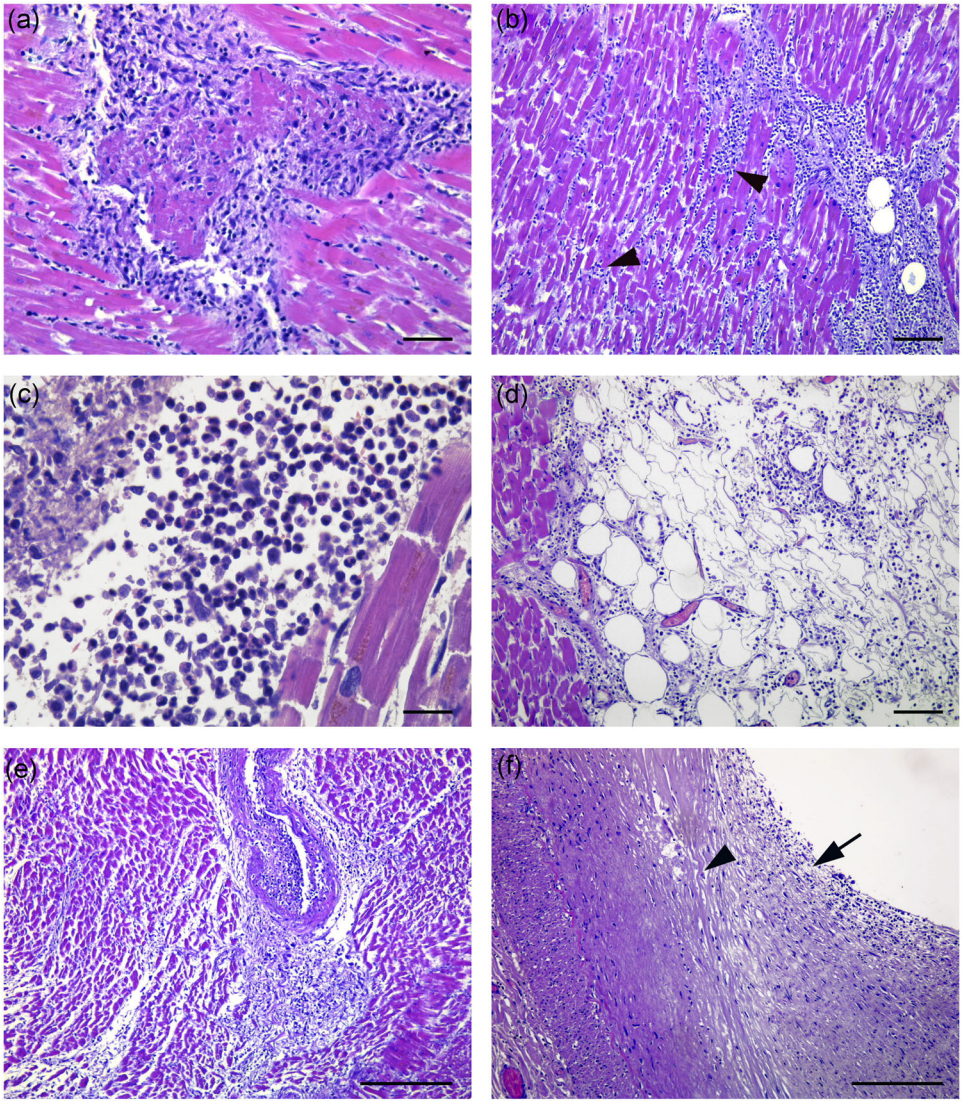

FIGURE 1 Pathological findings in the heart. (a–c) Active myocarditis characterized by lymphocytes, macrophages, neutrophils and eosinophils granulocytes associated with myocyte necrosis and myofiber disarray (arrowheads). (d) Pericarditis with lymphocytic inifiltration. (e) Necrotizing vasculitis with an inflammatory infiltrate formed by lymphocytes, monocytes, and eosinophils granulocytes. (f) Coronary artery with an inflammatory infiltrate of the tunica intima (arrow) and tunica media (arrowhead). H&E, haematoxylin and eosin. Scale bars: a = 28 μm; b, d = 56 μm; c = 14 μm; e, f = 200 μm

RIGHTSLINK

14401827, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/pin.13184 by University Di Roma La Sapienza, Wiley Online Library on [31/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

eosinophils (Figure S1c,d). Alveoli contained fibrin deposits admixed with macrophages, lymphocytes, and monocytes. Capillaritis and dystrophic calcification were present (Figure S1e,f). Other microscopic findings were ectasia of large-sized vessels, hyperplasia of the tunica intima and tunica media with fibrosis and pleuritis.

Lymphocytic inflammatory infiltrates, vasculitis and necrosis signs occurred also in histologic sections of the rectus abdominis muscle (Figure S2a).

The liver showed a nonalcoholic fatty liver disease consisting of diffuse microvacuolar and moderate panacinar macrovacuolar steatosis (G2, 33%–66% hepatocytes involved, according to Kleiner DE criteria),[3] associated with lobular and portal chronic inflammation, mostly lymphocytes, monocytes, and macrophages (Figure S2b). Fibrous enlargement of portal tract with septa formation was seen at Masson's trichrome stain.

The real-time polymerase chain reaction (RT-PCR) has been obtained from several frozen myocardial samples for the most common cardiotropic viral genomes, including CMV, EBV, HHV-6, enterovirus, and SARS-CoV-2. All tests were negative, except for HHV-6, which gave positive results on the myocardial sections. The RT-PCR result has been confirmed by immunofluorescence analysis (Figure S3).

Macroscopic and microscopic findings demonstrated that the fatal outcome was due to an HHV-6 related fulminant myocarditis. The patient presented clinical signs and symptoms consistent with a lot of viral infections, including COVID-19. If it is true that during the pandemic is important to exclude SARS-CoV-2 infection, particularly in patients with a suspicious clinical picture, remember that clinical signs are very similar to a lot of viral infections is equally so. Myocarditis is not only caused directly or indirectly by SARS-CoV-2,[4] but also by a lot of cardiotropic viruses that have to rule out.[5] In other words, in patients with suggested signs of viral infection, it is crucial to get screenings for all potentially causative pathogens. In the case at hand, the clinical course of fulminant myocarditis was, as usual, rapidly progressive and in just a few hours culminating in a fatal outcome. Consequently, the cause of death and the differential diagnosis of COVID-19 and other cardiotropic viruses were demonstrated by post-mortem examination.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the excellent support of the INMI pathology team: Alessia Brenna, Marco Canali, Mario Moauro, Nicolina Rotiroti, Wilfredo von Lorch, who risked SARS-CoV-2 infection in performing the autopsies and collecting the samples. We thank Concetta Castilletti, Laboratory of Virology, for kindly providing us the anti-HHV-6 antibody. This work was supported by grants from: the Italian Ministry of Health (Ricerca Corrente) and from "Associazione Unitaria Avvocati e Procuratori di Stato."

AUTHOR CONTRIBUTIONS

All authors contributed to the study design and data interpretation. Daniele Colombo and Franca Del Nonno collected autoptic specimens and performed histopathological analysis. Daniele Colombo and Camilla Cecannecchia wrote the paper. Daniele Colombo, Camilla Cecannecchia, Marco Albore, Fabrizio Taglietti, Roberta Nardacci, Giorgio Bolino, and Franca Del Nonno discussed the results and edited the manuscript. All authors contributed approved the final version.

DISCLOSURE

The authors declare no competing interests.

Daniele Colombo[1]
Camilla Cecannecchia[2]
Marco Albore[2]
Fabrizio Taglietti[3]
Roberta Nardacci[4,5]
Giorgio Bolino[2]
Franca Del Nonno[1]

[1]*Pathology Unit, National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Rome, Italy*
[2]*Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy*
[3]*Systemic and Immunocompromised Host Infection Unit, National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy*
[4]*Laboratory of Electron Microscopy, National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy*
[5]*UniCamillus – Saint Camillus International University of Health and Medical Sciences, Rome, Italy*

Daniele Colombo and Camilla Cecannecchia contributed equally to this study.

ORCID

Marco Albore http://orcid.org/0000-0003-3072-4459
Roberta Nardacci http://orcid.org/0000-0002-9209-1207

RIGHTSLINK

14401827, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/pin.13184 by University Di Roma La Sapienza, Wiley Online Library on [31/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

REFERENCES

1. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of Human Herpesvirus 6 infections. Clin Microbiol Rev. 2015;2:313–35.
2. Leveque N, Boulagnon C, Brasselet C, Lesaffre F, Boutolleau D, Metz D, et al. A fatal case of Human Herpesvirus 6 chronic myocarditis in an immunocompetent adult. J Clin Virol. 2011;2:142–5.
3. Kleiner DE. Histopathology, grading and staging of nonalcoholic fatty liver disease. Minerva Gastroenterol Dietol. 2018; 1:28–38.
4. Del Nonno F, Frustaci A, Verardo R, Chimenti C, Nicastri E, Antinori A, et al. Virus-negative myopericarditis in human coronavirus infection: report from an autopsy series. Circ Heart Fail. 2020;11:12–3.
5. Ginsberg F, Parrillo JE. Fulminant myocarditis. Crit Care Clin. 2013;3:465–83.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

14401827, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/pin.13184 by University Di Roma La Sapienza, Wiley Online Library on [31/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

RIGHTSLINK