

Acute heart failure due to COVID-19 related myocardial injury and *de novo* hypertensive cardiomyopathy: a challenging diagnosis

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Abstract

We report a COVID-19 case with acute heart and kidney failure in a healthy young male. Echocardiography showed severe systolic and diastolic left ventricle dysfunction, with diffuse myocardial thickening. Cardiac MRI showed aspects of focal myocarditis, and

hypertensive cardiomyopathy. Renal biopsy demonstrated limited acute tubular injury, and hypertensive kidney disease. Coronary angiography excluded critical stenoses. Unlike what we initially suspected, myocardial inflammation had a limited extent in our patient; severe hypertension causing cardiomyopathy and multi-organ damage, not diagnosed before, was primarily responsible for severe illness. Correct diagnosis and guidelines-directed treatment allowed a favorable course.

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Introduction

Coronavirus disease 2019 (COVID-19) is at the moment an international public health emergency, caused by a novel enveloped RNA beta-coronavirus, named 'severe acute respiratory syndrome coronavirus-2' (SARS-CoV-2). The infection is mainly characterized by respiratory tract symptoms, presenting as mild flu-like illness to potentially lethal acute respiratory distress syndrome or fulminant pneumonia, but relevant cardiovascular complications and multi-organ failure can occur in severe cases [1]. Patients with known cardiovascular disease and risk factors appear more vulnerable to the infection, and hypertension is highly prevalent in patients who develop severe illness. Pathological mechanism underlying this association is still not completely elucidated: binding of the virus to angiotensin-converting enzyme 2 receptor (ACE-2), highly expressed on endothelial surfaces, with consequent renin-angiotensin-aldosterone system deregulation, and cytokine storm seem to have a relevant role [2].

We report a case of acute HF and documented cardiac inflammation during COVID-19. Multi-modality cardiac imaging and a challenging interdisciplinary medical approach led to a *de-novo* diagnosis of hypertensive multi-organ damage, exacerbated by concomitant viral infection.

Case Report

A 45-year-old man presented to our Emergency Department in April 2020 for atypical chest pain, fever and worsening effort dyspnoea from 7 days before. His past medical history was unremarkable and he denied alcohol and/or drugs abuse. On his arrival high blood pressure (BP = 180/110 mmHg), bi-basal pulmonary rales and mild leg swelling were detected; oxygen saturation was 93% while breathing ambient air. Electrocardiography showed sinus tachycardia with left axis

deviation, slight diffuse ST depression more prominent in inferior-lateral leads (Figure 1A). Blood tests revealed a significant increase in Troponin T (82 ng/L; being 14 ng/L the upper reference limit of normal - URL), serum creatinine (3.1 mg/dl; eGFR 20 ml/min ml/min/1.73m²) and C-reactive protein (30 mg/L; being 5 mg/L the URL). At blood cell count, neutrophils were slightly augmented and lymphocytes slightly diminished. Nasopharyngeal swab was positive for SARS-CoV-2 infection. Chest X-rays and High resolution computed tomography scan of the lungs showed ground glass-like hyper density opacities limited to the peripheral portions of inferior lobes bilaterally, and a small area of consolidation in the left superior lobe (Figure 1 B,C). Transthoracic echocardiography was also performed and showed mild increase in LV dimension (end diastolic diameter: 57 mm; end diastolic volume: 141 ml, 83 ml/m² BSA) and moderate increase in walls thickness (interventricular septum = 13.5 mm; posterior wall = 11 mm), with a sparkling appearance. LV ejection fraction (LVEF) was severely reduced because of a diffuse parietal hypokinesia (LVEF = 30%; quantified by Simpson's method). Left atrium was moderately enlarged (volume=73 ml, 43 ml/m² BSA), and the mitral diastolic filling pattern was restrictive. There was a mild mitral and tricuspid regurgitation and a mild pericardial effusion was noted behind the inferior-lateral LV wall. A few hours after admission to our cardiac intensive care unit, patient's condition degenerated abruptly; he presented BP elevation to 210/130 mmHg and respiratory failure, requiring nitroglycerine infusion, high doses of intravenous furosemide and non-invasive ventilatory support with continuous positive airway pressure (CPAP) of 10 cm H₂O. From the next days, clinical conditions began to improve, allowing removal of CPAP on

day 3. Therapy with bisoprolol was initiated and gradually titrated up to 3.75 mg/die; amlodipine 10 mg/die and alfuzosin 2 mg bid were also introduced for BP control. For viral infection, hydroxychloroquine (200 mg bid) and darunavir/ritonavir (800/100 mg od) were administered for 10 and 5 days respectively according to local protocol. Feverish episodes (temperature >38°C) persisted for the first 4 days. Clinical laboratory tests trend during hospitalization is summarized in Table 1. Notably, serum creatinine remained constantly elevated; there was modest proteinuria (228 mg/L), without Bence-Jones proteinuria; serum and urine protein immunofixation excluded monoclonal free light chains.

When patient's clinical conditions were stable, echocardiogram was repeated and confirmed diffuse parietal hypokinesia with improvement in LV systolic and diastolic function (LVEF = 38% and 'pseudonormal' diastolic filling pattern) (Figure 2). Diffuse myocardial thickening was still evident. 2D Speckle-tracking showed diffuse reduction of global longitudinal strain, more severe in anterior segments, and partial apical sparing. Cardiac magnetic resonance imaging (MRI) was performed, showing increased symmetric and circumferential wall thickness, with diffuse LV hypokinesia (LVEF 35%) and mild hypokinesia of right ventricle (RVEF 41%). Short tau inversion recovery and T2-Mapping sequences demonstrated the presence of focal myocardial oedema, in medium and apical segments of anterior wall and anterior septum. Phase-sensitive inversion recovery sequences showed a diffuse and intramural late gadolinium enhancement (LGE) of LV myocardium in all segments, with circumferential distribution. Pericardial effusion was not present (Figure 3). This pattern resulted appeared consistent with hypertensive cardiomyopathy, and myocarditis of

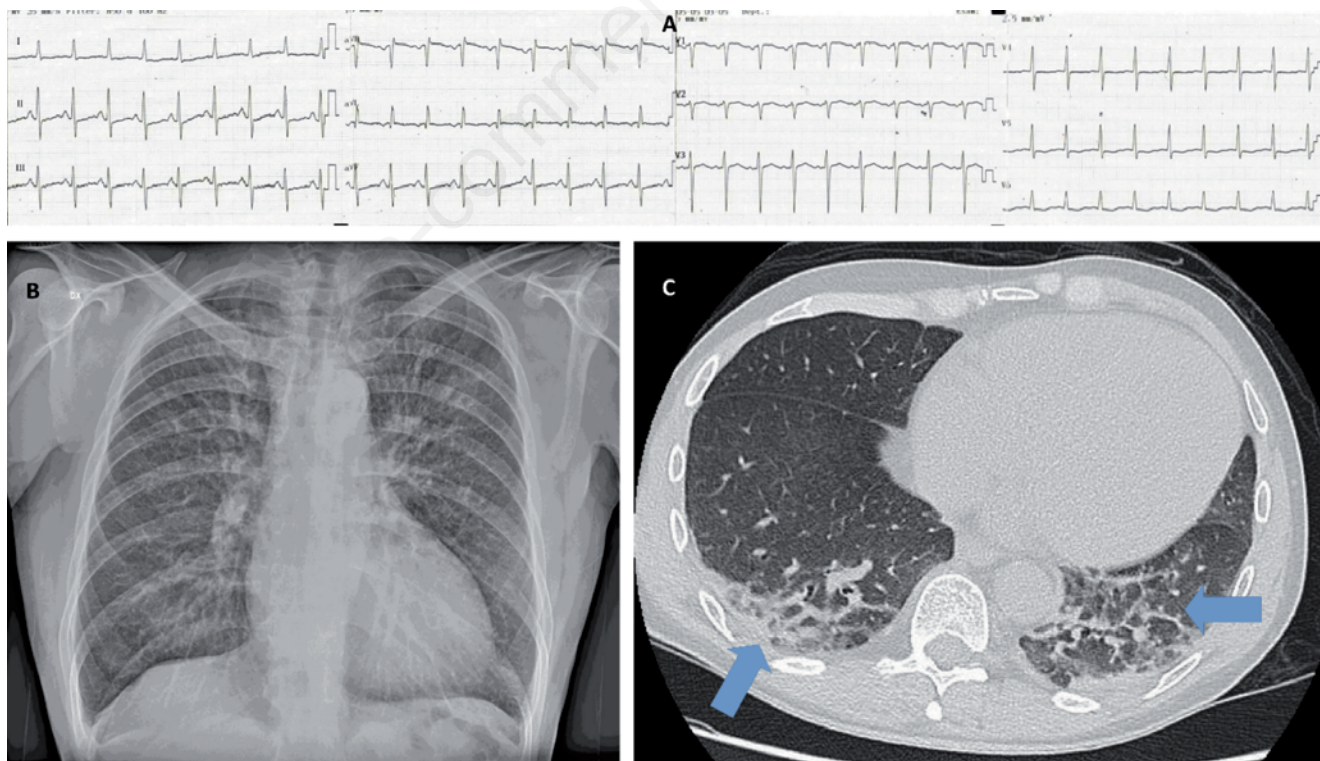


Figure 1. A) Electrocardiogram on admission. Sinus tachycardia with left axis deviation, slight diffuse ST depression more prominent in inferior-lateral lead. B) Chest X-ray. Interstitial oedema limited to left superior and lateral regions, and no pleural effusion. C) Image from high resolution computed tomography scan of the lungs. Ground glass-like hyper density opacities in the peripheral portions of inferior lobes bilaterally (arrows).

limited extent. The day after, the patient underwent cranial computed tomography, showing multiple ischemic lacunar foci of the basal ganglia bilaterally, a stabilized ischemic lesion of the right corona radiata and white matter hypodensity (Supplementary figure 1). Doppler ultrasound excluded clinically relevant carotid stenosis, and significant renal arteries pathology. Renal biopsy demonstrated diffuse acute tubular injury and modest chronic interstitial inflammation, with minimal tubulitis. Severe arteriolar hyalinosis (also in preglomerular arterioles), glomerular capsular thickening and capillary basement membrane wrinkling and duplication were also present, as for chronic hypertensive kidney disease (Figure 4). Amyloid deposits were excluded. Fifteen days after admission, the patient was discharged. One month later, after clinical and biochemical resolution of COVID-19 as demonstrated by two consecutive negative nasopharyngeal swabs, he was readmitted in our Unit for coronary angiography control. This showed diffuse atherosclerotic disease of epicardial vessels without critical stenoses (Supplementary Figure 2). A new echocardiogram demonstrated further reduction of LV volumes with improvement in EF (to 46%). Assessment of left ventricular filling demonstrated an abnormal relaxation pattern (grade I diastolic dysfunction). Renal function was persistently impaired (serum creatinine: 2.9 mg/dl). Cardiac MRI performed 2 months later, showed a reduction in biventricular volumes with improvement in LVEF up to 50%; LV parietal hypertrophy was unchanged (septal thickness: 13 mm) with mild, diffuse intramural LGE; T1 and T2 sequences showed oedema resolution.

Discussion

The present report describes a case of COVID 19 with acute respiratory failure, acute myocardial and kidney injury, in a patient firstly diagnosed with severe hypertension causing dilated cardiomyopathy and multiple target-organ damage. Definite diagnosis was possible through myocardial and renal tissue characterization. Notably, they were both obtained in a living patient with severe COVID 19, the first through cardiac magnetic resonance, the latter by means of kidney biopsy. Pre-existing CV disease were found to be independent predictor of in-hospital mortality in COVID-19 patients [1-3]. Moreover, severe illness may be complicated by acute myocardial injury, clinically expressed by electrocardiographic abnormalities, myocardial dysfunction and troponin release, being associated with a worse prognosis [4,5]. Cardiac involvement may occur due to ischemic (acute myocardial ischemia/infarction) or non-ischemic processes, including stress-induced cardiomyopathy and myocarditis.

Several cases of acute heart failure or cardiogenic shock caused with echo-documented and MRI-proven myocardial inflammation due to COVID-19 have been published so far [6-8]; cardiac MRI showed diffuse, extensive myocardial oedema conditioning global cardiac function impairment. In our case, echocardiography during hospitalization showed diffuse myocardial thickening, with an echobright appearance, severe diastolic dysfunction with initially restrictive filling pattern, bi-atrial enlargement and mild pericardial

Table 1. Laboratory tests during hospitalization.

Measure	Reference range	Results							
		Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	
Haemoglobin, g/dL	14.2-17.2	14	12.6	12	11.5	11.9	12	12.4	
White blood cell count, 10 ⁹ /L	4.2-9.4	8.98	7.26	7.24	7.46	7.01	7.63	9.66	
Lymphocyte relative count, %	19.6-46.5	14.6	16.8	16.9	10.2	27.5	33.6	29.0	
Lymphocyte absolute count, 10 ⁹ /L	1.1-3.4	1.31	1.22	1.22	0.76	1.93	2.56	2.81	
Neutrophil relative count, %	40.6-68.4	82	79	77	85	65	58	60.8	
Neutrophil absolute count, 10 ⁹ /L	2-5.8	3.2	5.73	5.58	6.3	4.57	4.46	2.91	
Platelet count, 10 ⁹ /L	155-320	273	224	197	186	267	353	500	
D-dimer, ug/L	<500	1026	1865	875	889	863	821	795	
Creatinine, mg/dL	0.7-1.2	3,1	3,03	3.3	3.2	2.9	2.7	2.9	
eGFR, ml/min/1,73m ²		21	22	20	21	24	25	24	
Sodium, mmol/L	136-145	134	135	130	133	131	138	135	
Potassium, mmol/L	3.5-5.1	2.35	2.5	2.5	3.1	3.7	4.3	4.4	
Aspartate aminotransferase	<40	22		54		28		43	
Alanine aminotransferase	< 40	16		15		19		45	
Hs-troponin T, ng/L	<14	89	97	109	107	84	80	35	
C-reactive protein, mg/dL	<5	30	54	150	104	79	43	25	
Il-6, pg/ml	0-7			47.4				28.9	
Serum Kappa light chains, mg/L	3.3-19.4							168	
Serum Lambda light chains, mg/dL	5.7-26.3							98	
Free light chain ratio	0.26-1.65							1.7	
Bence Jones proteinuria								Absent	
Urinary proteins, mg/L	0-150						228		
Immunofixation of urine proteins		No monoclonal free light chains; tubular proteinuria							
Immunofixation of serum proteins		No monoclonal free light chains							

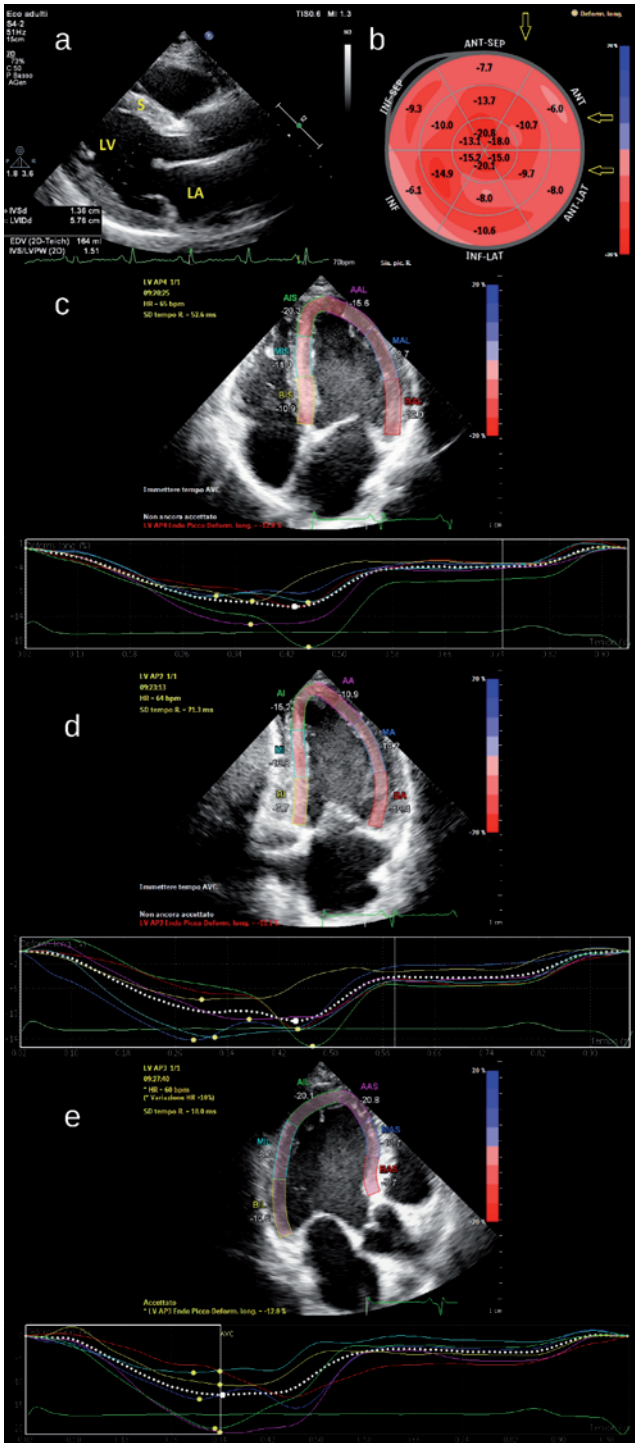


Figure 2. Echocardiogram performed on day 10th. A) Parasternal long-axis view, showing moderate concentric LV hypertrophy with echo-bright appearance of myocardium. LV, left ventricle; S, septum; LA, left atrium. b-e) 2D-speckle tracking longitudinal strain evaluation. b) Bull's eye with global results; global longitudinal strain: -12% (18 segments); diffuse hypokinesia is evidenced, more pronounced in basal anterior and septal segments (arrows), and relative apical sparing. c,d,e) Longitudinal strain evaluated in apical 4-chamber, 2-chamber, and 3-chamber views, respectively, with strain curves for each segment.

effusion. Moreover, global longitudinal strain with partial apical sparing was detected at 2D-speckle tracking. These aspects aroused at first the suspect of a possible infiltrative cardiomyopathy, as amyloidosis. Other diagnostic hypotheses were: extensive COVID-19 related myocardial inflammation with diffuse interstitial infiltrates, or misdiagnosed hypertensive cardiomyopathy. Systemic amyloidosis was also at first suggested by the presence of kidney failure, but this hypothesis was later rejected on the basis of serum and urine immunofixation. Cardiac MRI was crucial in the diagnostic process; it confirmed diffuse myocardial thickening and systolic impairment; myocardial oedema depicted by T1 and T2 sequences had a limited extent, thus suggesting that the severe cardiac impairment was not exclusively caused by myocarditis.

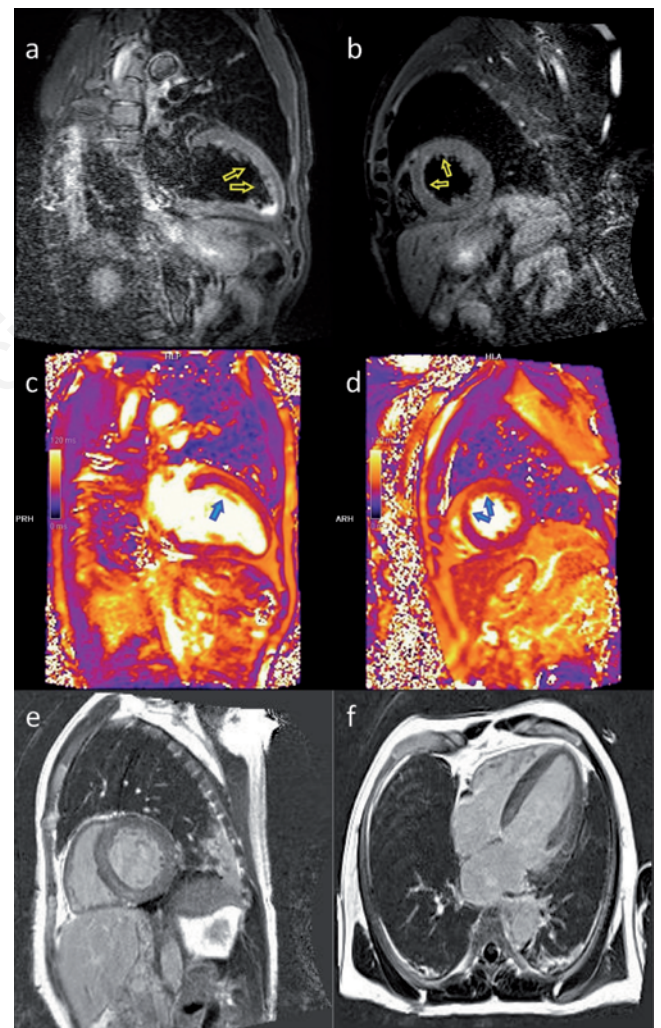


Figure 3. Cardiac magnetic resonance imaging. Short tau inversion recovery (STIR) sequences in 2-chamber (A) and short-axis view (B) showed mild myocardial signal hyperintensity in left ventricle anterior wall and anterior septum in medium and apical segments (arrows), consistent with interstitial oedema, confirmed and best depicted in corresponding T2-Mapping sequences (C and D, arrows). Phase sensitive inversion recovery (PSIR) sequences in short-axis (E) and 4-chamber view (F) showed diffuse intramural late gadolinium enhancement.

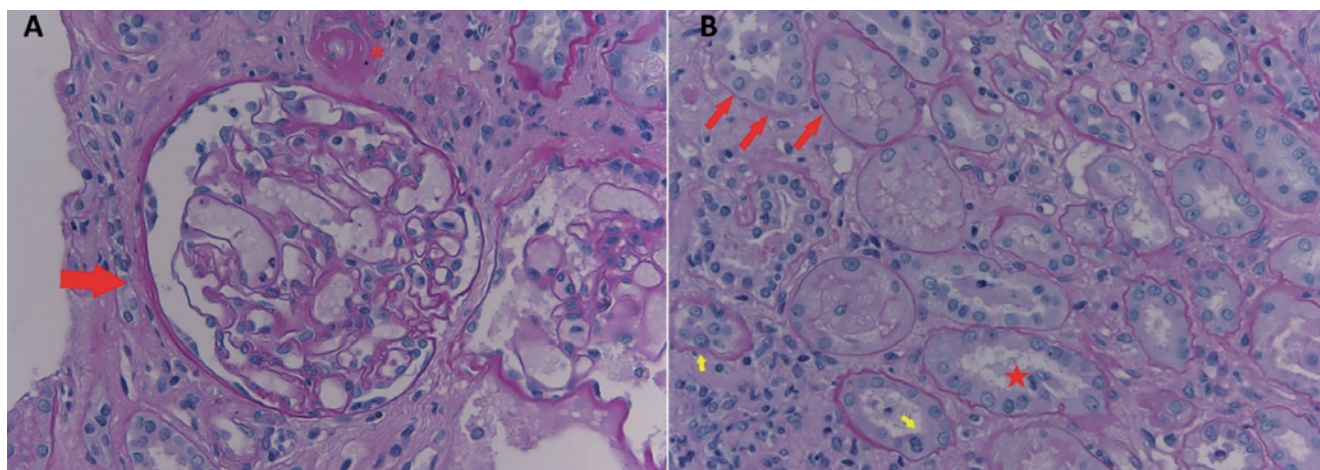


Figure 4. Renal biopsy specimens, PAS (Periodic Acid Schiff) stain. **A)** Capsular thickening and wrinkling of glomerular basement membrane (arrow). Circumferential arteriolar hyaline sclerosis (asterisk). **B)** Diffuse acute tubular injury with brush border loss, tubular dilatation, epithelial thinning or swollen, focal vacuolization (red arrows); partial desquamation of tubular epithelial cells (star); focal regeneration features (prominent nucleoli and mitosis – yellow arrows); modest interstitial chronic inflammation with minimal tubulitis.

LGE pattern appeared non suggestive for amyloidosis and supported the diagnosis of hypertensive cardiomyopathy. Interestingly, cardiac function gradually improved during and after hospitalization, in parallel with COVID-19 resolution and effective treatment of hypertension.

Kidney impairment is frequent in COVID-19 patients: more than 40% of them have proteinuria at hospital admission [9], while some critically ill patients may develop during hospitalization an acute kidney injury (AKI) [10]. The most common pathogenic factors appear related to direct renal injury (promoted by the binding of SARS-CoV-2 to ACE-2 on tubular cells and podocytes), to microthrombi formation due to hypercoagulability, and to the effects of acute systemic inflammatory response [10]. Kidney biopsy findings in our patient revealed diffuse acute tubular damage with modest interstitial inflammation, as for AKI, together with glomerular and vascular alterations consistent with chronic hypertensive nephropathy. Resolution of infective process however did not lead to a significant improvement of kidney function; thus, we can speculate that in this patient the long-time undiagnosed severe hypertension was the main contributor to his kidney impairment. Cranial CT findings, suggestive for hypertensive encephalopathy, were also in keeping with a severe uncontrolled hypertension not diagnosed before.

In conclusion, our report depicts how a condition of severe, untreated hypertension can increase cardiac vulnerability to COVID-19 infection: acute inflammatory alterations, even of limited extent, may critically destabilize a pre-existing organ damage of hypertensive aetiology, leading to a condition of severe HF. This report highlights that in these patients the same mechanistic approach to cardiac and systemic abnormalities should be used, increasing utilization of multi-modality imaging and diagnostic tools that may help us to make a correct diagnosis.

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