

From post-COVID-19-associated myocarditis to hemopericardium: a dangerous domino effect

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The majority of patients infected with Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) either completely recover from symptoms in a few days or stay asymptomatic.^[1–3] Nevertheless, a consistent proportion of subjects with a history of probable or confirmed SARS-CoV-2 infection refers persistency, new occurrence, relapse, or fluctuation of symptoms, and these manifestations are defined as post-COVID-19 condition.^[4] Of note, the post-acute sequelae of COVID-19 include several cardiac manifestations, including direct myocardial and pericardial injury/inflammation, as well as cardiomyopathies and arrhythmias, sustained by viral infiltration and/or dysregulation of adaptive immune response.^[5] Even though rare, acute myocarditis may be an important post-COVID-19 condition and may be associated with the occurrence of new-onset atrial fibrillation.^[6,7] Even though no defined indications related to anticoagulation in COVID-19 patients with new-onset atrial fibrillation are available, direct oral anticoagulants (DOACs) have represented the preferred choice of several physicians during the pandemics, due to their favorable pharmacological profile.^[8,9] Indeed, DOACs show better efficacy and safety profile as compared to warfarin in atrial fibrillation, especially considering life-threatening and intracranial bleeding.^[10] Spontaneous hemorrhagic pericardial effusion is a rare bleeding complication which occurs in 2.5%–11% patients treated with DOACs.^[11] Herein, we describe a case of an 82-year-old patient

hospitalized because of a post-COVID-19 pneumonia. During hospitalization, acute myocarditis with new-onset atrial fibrillation were diagnosed. She was treated with apixaban to prevent thromboembolic complications, but hemorrhagic pericardial effusion with cardiac tamponade occurred after seven days.

Figure 1 reports the timeline of this case. On 21 January 2023, an 82-year-old woman living at home presented to the Emergency Room of our Hospital with dyspnea and thoracic pain. Her medical history included rheumatoid arthritis, hypertensive heart disease, hiatal hernia, colonic diverticulosis, dorsal and lumbar spondylosis, mild cognitive impairment, and generalized anxiety disorder. She reported to be affected by paucisymptomatic COVID-19 infection in December 2022 (negative SARS-CoV-2 antigen test on 31.12.2022). She was on daily oral treatment with losartan 100 mg, hydrochlorothiazide 25 mg, acetylsalicylic acid 100 mg, carvedilol 12.5 mg, atorvastatin 20 mg. Physical examination revealed normal vital signs and respiratory rate, reduced vesicular sounds at the lower lung fields without any pathological noises on chest auscultation. Chest-X-ray displayed basal bilateral thickening and left costophrenic angle obliteration (Figure 2). The antigenic test on the nasopharyngeal swab revealed the absence of SARS-CoV-2. Laboratory results on admission showed neutrophilic leukocytosis, and increased C-reactive protein, procalcitonin, D-dimer and N-Terminal Brain Natriuretic Peptide

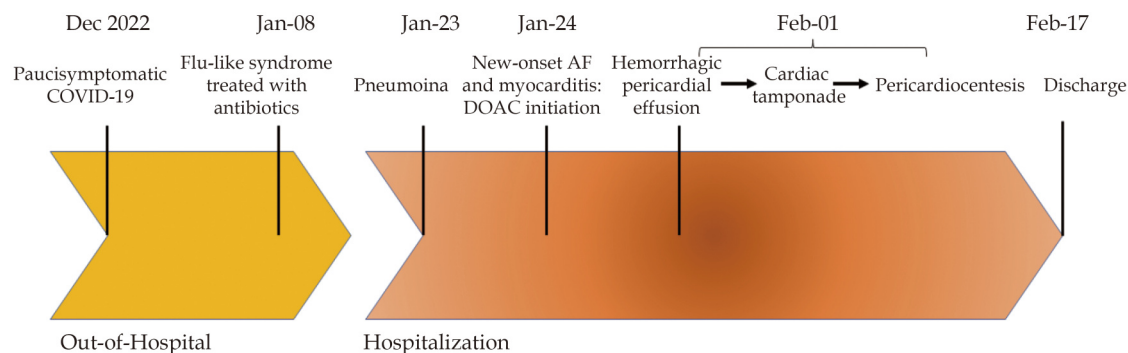


Figure 1 Case report timeline.



Figure 2 Chest X-ray taken on admission, showing basal bilateral pleural thickening and left costophrenic angle blunting.

(Table 1). The patient was hospitalized with a diagnosis of pneumonia and treated with ciprofloxacin 500 mg (b.i.d.), ramipril 2.5 mg, carvedilol 6.25 mg (b.i.d.), acetylsalicylic acid 100 mg, atorvastatin 20 mg, memantine 20 mg.

The day after hospitalization, the patient presented with sudden thoracic pain, dyspnea and palpitations, she was tachycardic at 125 beats/min, her blood pressure was 75/50 mmHg and her oxygen saturation (SpO_2) was 88% on room air. ECG showed atrial fibrillation and no modifications of the ST segment. Transthoracic echocardiogram showed left ventricular thickening (septal thickness 1.6 cm) with aspects of edema, but the left ventricular ejection fraction and wall motion were within normal limits (Figure 3). Laboratory results showed raised high sensitivity troponin T and myoglobin, and partial respiratory failure (Table 1). A coronary angiography was performed, with no evidence of coronary artery disease. Overall, these findings suggested myocarditis. An autoimmune screen and viral sero-

logy for potential causes of myocarditis were ruled out and returned negative. The patient was started on intravenous noradrenalin and amiodaron, oxygen therapy, anticoagulation with apixaban, and ciprofloxacin was replaced with piperacillin/tazobactam.

The patient's conditions improved significantly during the following days, normal sinus rhythm was restored, intravenous noradrenalin and amiodaron were discontinued and she was started on oral amiodaron 200 mg, oxygen therapy was progressively reduced, and at the 9th day after hospitalization she was ready to be discharged (Table 1). Nevertheless, the patient presented sudden dyspnea, tachypnea (respiration rate 25 breaths per minute), fatigue, malaise, and retrosternal pain. A new transthoracic echocardiogram was performed, showing moderate-severe pericardial effusion with right ventricle diastolic collapse, suggestive of cardiac tamponade (Figure 4). The patient underwent pericardiocentesis, and 700 mL of hematic pericardial fluid were drained. Pericardial fluid analysis showed red, cloudy fluid with erythrocyte predominance. Other tests from pericardial fluid such as adenosine deaminase (ADA), bacterial and mycobacterial cultures, as well as SARS-CoV-2 polymerase chain reaction (PCR) test were negative.

Anticoagulation therapy was stopped and during the hospital course the patient showed progressive clinical improvement, without any further episode of atrial fibrillation. 16 days after pericardiocentesis, a transthoracic echocardiogram described a residual and partially organized pericardial effusion, and the patient was discharged for cardiology follow-up.

The main linchpin of medicine consists in the exact detection of the cause of a disease, not only to use



Table 1 Laboratory results.

Variable	Reference range	Admission	Day 1	Day 9	Discharge
C-reactive protein, mg/L	0.0-5.0	151*	220*	55.6*	24.9*
HS-Troponin I, ng/L	< 10.8	2.7	2148.4*	1347.7*	5.1
Myoglobin, ng/mL	17.4-105.7	37.6	201.3*	178.1*	22.3
D-dimer, ng/mL	< 500	1022*	1229*	7121*	7145*
Sodium, mmol/L	136-146	139	142	138	139
Potassium, mmol/L	3.5-5.3	3.8	3.1 [#]	3.9	5.1
Chloride, mmol/L	97-110	100	100	96	103
Oxygen, mmHg	> 80	71 [#]	33 [#]	63 [#]	70
Carbon dioxide, mmHg	35 - 45	39	44	36	35
Bicarbonates, mmol/L	22-26	28.4*	27.9*	30.1*	26.9*
Blood urea nitrogen, mg/dL	10-50	60*	91*	56*	45
Creatinine, mg/dL	0.20-1.10	1.10	1.0	1.02	1.05
Glucose, mg/dL	70-110	132*	89	107	108
Calcium, mg/dL	8.8-10.6	9.4			8.9
Total protein, g/dL	6.1-8.3	7.0			6.3
Albumin, g/dL	3.2-5.0	3.27			
Globulin, g/dL		0.5			
Aspartate aminotransferase, U/L	2-40	18	13		
Alanine aminotransferase, U/L	2-40	13	20		
Total bilirubin, mg/dL	0.2-1.2	0.86	1.08		
Gamma glutamyl-transpeptidase, U/L	7-38	13	12		
Alkaline phosphatase, U/L	30-120	78	76		
Procalcitonin	< 0.5	2.8*	2.16	0.14	< 0.05
White-cell count, per mm ³	4000-10000	14790*	25350*	11040*	11010*
Hemoglobin, g/dL	12-16	13.4	12.6	11.6 [#]	12.1
Hematocrit	36%-48%	41.8%	36.8%	34.7% [#]	36.8%
Platelet count, 1000 per mm ³	130-450	291	258	439	421
Absolute neutrophil count, per mm ³	1.6-6.5	12.20*	22.81*	8.51*	9.73*
Absolute lymphocyte count, per mm ³	0.8-4.5	1.35	1.14	1.38	1.55
NT-BNP, pg/mL	< 300	4080*			1170*

*The value in the patient was above the normal range. [#]The value in the patient was below the normal range. HS: high sensitivity; NT-BNP: N-terminal brain natriuretic peptide.

the best diagnostic exam, but also to allow the most suitable therapy. This report describes the case of an old lady hospitalized for post-COVID-19 pneumonia, presenting with new-onset atrial fibrillation who was subsequently found to have echocardiographic signs consistent with myocarditis; after the introduction of anticoagulation therapy, the patient experienced hemorrhagic pericardial effusion with cardiac tamponade. The course of this case can be represented as a concrete sequence of events, according to the singular causation theory^[12] (Figure 5).

A considerable percentage of patients previously affected by COVID-19 may present with cardiopulmonary manifestations, including palpitations, dyspnea, thoracic pain, and cardiac arrhythmias which occur after weeks or months after the acute SARS-CoV-2 infection.^[13] Myocarditis, defined as a non-ischemic inflammatory condition of the myocardium, is often caused by viral infections but also post-viral immune-mediated responses.^[14] The most accredited hypothesis to support myocardial injury triggered by SARS-CoV-2 is not related to direct vir-



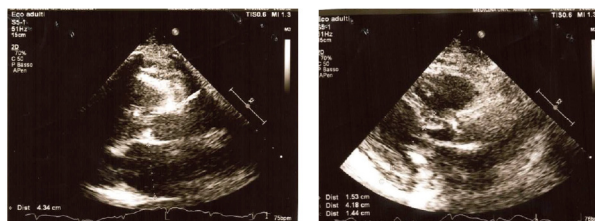


Figure 3 Transthoracic echocardiogram the day after hospitalization, showing left ventricular hypertrophy.

al infection of cardiomyocytes – since viral RNA is not detectable in cardiac cells^[15] – but is explained by hyperactivation of the immune response.^[16] Indeed, dysregulation of lymphocytes caused by molecular mimicry between the host and the virus or by virus-related modified self-proteins may explain immune-mediated myocardial injury.^[17] Serology tests for conventional causes of myocarditis – including human herpes virus, Epstein-Barr virus, cytomegalovirus, parvovirus B19, adenovirus, HIV, and hepatitis C virus – as well as autoantibody screen resulted negative in our patient. However, since the association between COVID-19 and myocarditis is not frequent, and acute coronary syndrome represents the most important differential diagnosis,^[18] the patient was subjected to a coronary angiograph which resulted negative. Even though endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, this exam was not performed because the patient showed no signs of heart failure. Thus, we concluded that previous COVID-19 infection was the most likely cause of myocarditis and new-onset atrial fibrillation in our patient.

During myocarditis, several arrhythmias may occur as a manifestation of altered electrical activity.^[19] Among them, new-onset atrial fibrillation is the most frequently reported.^[20] Since both COVID-19 and atrial fibrillation increase the risk of thrombotic disorders *via* activation of thrombo-inflammatory

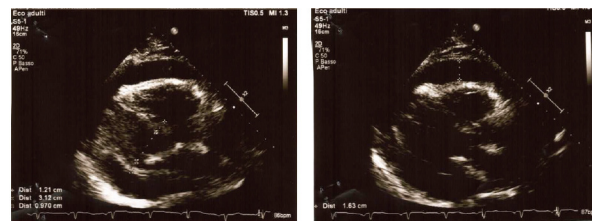


Figure 4 Transthoracic echocardiogram ten days after hospitalization, showing moderate-large pericardial effusion with diastolic collapse of right cardiac chambers.

pathways, introduction of anticoagulation therapy is strongly encouraged.^[21] DOACs represent the most recommended drugs for the management of thromboembolic risk in patients with non-valvular atrial fibrillation.^[22] When compared to warfarin, DOACs show a lower bleeding profile particularly related to life-threatening and intracranial hemorrhages.^[23] Among the infrequent hemorrhagic complications related to the use of DOACs, spontaneous pericardial bleeding has not been comprehensively reported, occurring in 2.5%-11% of patients – mostly treated with rivaroxaban.^[11] A recent systematic review on hemorrhagic pericardial effusion in patients treated with DOACs concluded that hemopericardium in this setting has a favorable outcome, but it often requires pericardiocentesis.^[24] Factors linked with high risk of hemorrhagic pericardial effusion include male gender, older age, renal failure, and coagulation alterations, and bleeding time may range from 2 days to 6 months after DOAC initiation.^[25] Considering the Naranjo Adverse Drug Reaction Probability Scale, this case reports a “probable” association between apixaban and hemopericardium.^[26] The increased bleeding risk in our patient may also be attributed to the concomitant initiation of amiodarone since it can reduce the metabolism of apixaban and increase its serum concentration.^[27] Furthermore, a relationship between myocarditis and

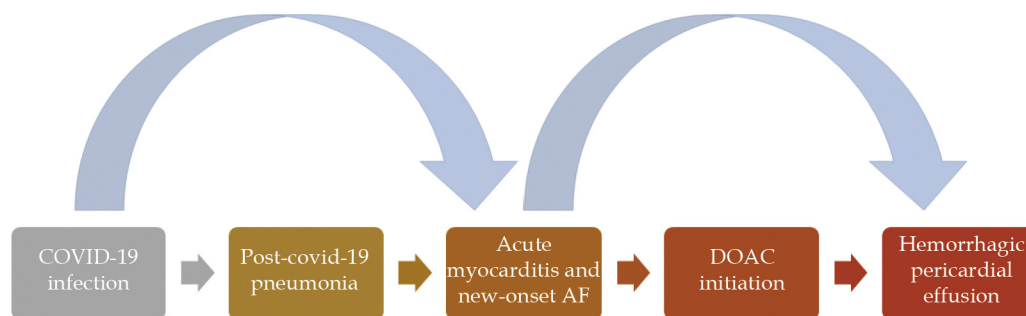


Figure 5 Diagrammatic representation of the effective causal complexes, according to the case report.

pericardial bleeding in the setting of post-COVID-19 cannot be excluded since pericardial effusion and cardiac tamponade were already described in COVID-19 patients.^[28]

To conclude, this case report highlights evidence of acute myocarditis as a post-COVID-19 presentation, which may be sustained by immune-mediated mechanisms or late cytotoxic effects, even though the exact molecular pathways need to be demonstrated. Moreover, this case describes hemorrhagic pericardial effusion as a potential, albeit rare, side effect of DOAC initiation. Notwithstanding the need of substantial investigations, we recommend monitoring post-COVID-19 patients with predisposing factors to show potential cardiac manifestations such as myocarditis and new-onset atrial fibrillation. In this setting, special caution should be adopted when introducing DOACs to prevent thromboembolic events, to avoid a causal chain effect that can potentially lead to life-threatening bleeding events.

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