ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–6
https://doi.org/10.1093/ehjcr/ytac199

CASE REPORT
Heart failure

Cardiovascular complications of catastrophic antiphospholipid syndrome: a case report and review of literature

Nitish Mittal [1†], Mostafa Abohelwa [2†], M. Rubayat Rahman[3], and Scott Shurmur[3]*

[1]Texas Tech University Health Science Center, School of Medicine, Class 2022, Lubbock, TX, USA; [2]Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA; and [3]Internal Medicine Department, Cardiology Division, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Received 30 November 2021; first decision 21 January 2022; accepted 9 May 2022; online publish-ahead-of-print 11 May 2022

Background Antiphospholipid syndrome (APS) is an autoimmune response characterized clinically by arterial or venous thrombosis. One of the rare and series forms of APS is the catastrophic APS (CAPS). The incidence of CAPS has been reported in 0.8% of patients with APS. There have been very few case reports with cardiac involvement in CAPS. Common cardiac manifestations include valvular thickening and lesions, coronary artery disease, and myocardial infarction due to microvascular thrombosis. Here, we are reporting a case of CAPS associated with heart failure and a literature review of similar cases.

Case summary A 24-year-old woman with a history of APS presented with shortness of breath and right-sided pleuritic chest pain. Computed tomography pulmonary angiogram revealed new pulmonary emboli in the right lung. After 5 days, she developed high-grade fever with negative infectious workup, acute hypoxic respiratory failure with pulmonary oedema, shock, acute kidney injury, and transthoracic echocardiography showed reduced ejection fraction and global hypokinesia. The constellation of multi-organ failure, symptoms within a week, the presence of antiphospholipid antibodies, and exclusion of other causes, CAPS was diagnosed. The patient showed significant improvement with pulse steroids, IV plasmapheresis and got discharged on oral prednisone taper and anticoagulation with home health.

Conclusion There are different cardiac complications associated with CAPS, including congestive heart failure, acute coronary syndrome, valvular lesions, and thrombus. Heart failure management in CAPS includes triple therapy of intravenous immune globulin, IV plasmapheresis, and corticosteroids rather than conventional treatment.

Keywords Catastrophic antiphospholipid syndrome • Congestive heart failure • Case report • Literature review

ESC Curriculum 6.2 Heart failure with reduced ejection fraction • 9.4 Thromboembolic venous disease • 2.2 Echocardiography • 7.1 Haemodynamic instability • 6.4 Acute heart failure

* Corresponding author. Tel: +1 806 743 1501, Email: Scott.shurmur@ttuhsc.edu
† Both authors contributed equally to the manuscript.
Handling Editor: Sameh Shaheen
Peer-reviewers: Edin Begic; Kyriakos Dimitriadis; Deborah Cosmi
Compliance Editor: Daniel Tardo
Supplementary Material Editor: Jonathan Senior

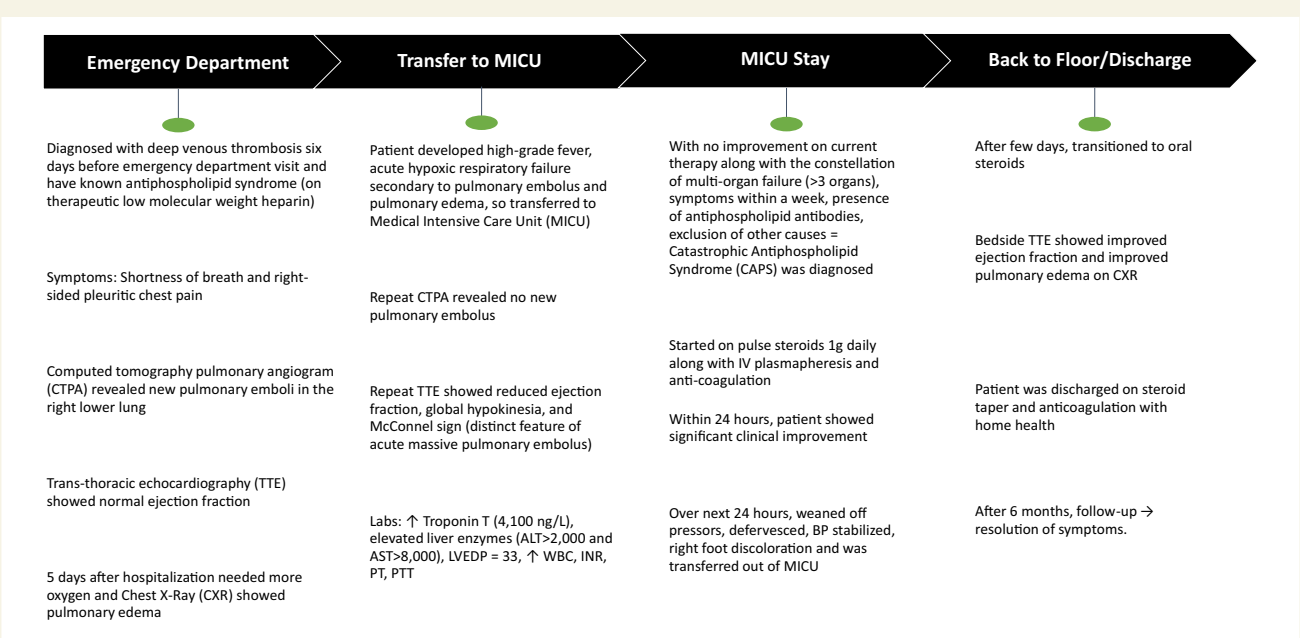
Learning points

- The definitive criteria for catastrophic antiphospholipid syndrome include the involvement of three or more organs, the development of clinical manifestations within a week, histopathological evidence of small vessel occlusion, and the presence of antiphospholipid antibodies.
- Cardiovascular complications observed were reduced ejection fraction of 40-45%, global hypokinesia, and myocardial infarction with non-obstructive coronary arteries likely from microvascular thrombosis.
- The cardiovascular complications in the case were resolved with pulse steroids and IV plasmapheresis rather than conventional heart failure treatment.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune response characterized clinically by arterial or venous thrombosis. One of the rare and serious forms of APS is the catastrophic APS (CAPS). The CAPS is associated with expeditious development of multi-system microvascular thrombosis in patients with antiphospholipid antibodies (aPLs).[1] Patients may present with heart failure, acute kidney injury, shock, and even death. Epidemiological studies performed in the USA and Italy confirmed the low prevalence of APS, identified in 17–50 patients per 100 000.[2] The incidence of CAPS is extremely rare and has been reported in 0.8% of patients with APS.[3] There have been very few case reports with cardiac involvement in CAPS. Common cardiac manifestations include valvular thickening and lesions, coronary artery disease, and myocardial infarction due to microvascular thrombosis.[4] Here, we describe a case of CAPS in a 24-year-old woman complicated by congestive heart failure.

Timeline



Case presentation

A 24-year-old woman known to have APS presented to the emergency department (ED) with shortness of breath and right-sided pleuritic chest pain of a few days duration. She was diagnosed with deep vein thrombosis in the right profunda femoris vein 6 days before the ED visit and was started on therapeutic low molecular weight heparin. In the ED, computed tomography pulmonary angiogram (CTPA) protocol was performed and revealed new pulmonary emboli in the right lower lung. Initial electrocardiography (ECG) showed sinus tachycardia (*Figure 1*). She got admitted to the hospital and the anticoagulation was switched from low molecular weight heparin to heparin drip. Initial transthoracic echocardiography (TTE) was done and showed normal ejection fraction (see Supplementary material online, *Video 1*). However, after 5 days of hospitalization, her condition suddenly deteriorated, and she required more oxygen. Chest X-ray was done and showed pulmonary oedema (*Figure 2*). She also started to develop high-grade fever with worsening of her oxygenation to the point that she required high flow nasal cannula. She was started empirically on broad spectrum antibiotics, but the

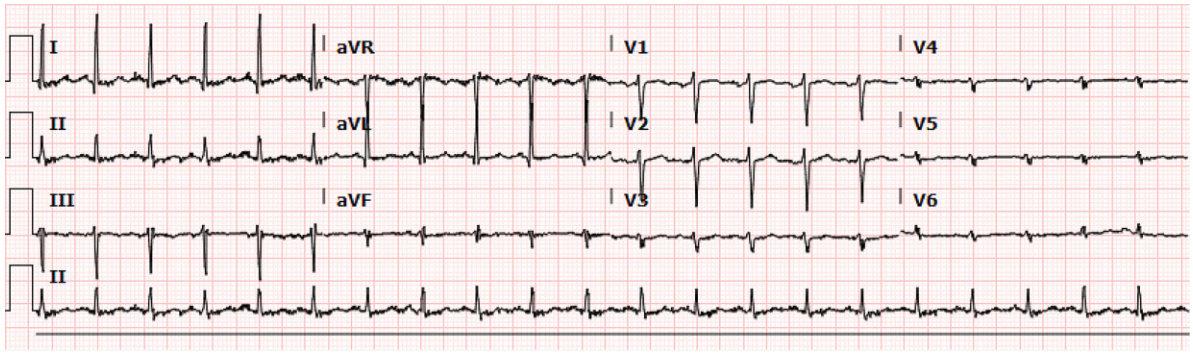


Figure 1 Electrocardiogram showing sinus tachycardia.

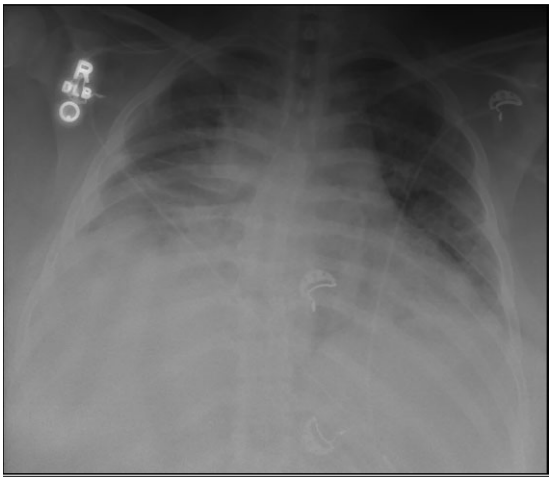


Figure 2 Chest X-ray showing pulmonary oedema.

infectious workup was negative including respiratory virus panel, blood cultures, urine, and sputum culture. She was transferred to the medical intensive care unit (MICU) due to acute hypoxic respiratory failure secondary to acute pulmonary embolus and pulmonary oedema. In the first day of her MICU stay, CTPA was repeated and ruled out any new pulmonary emboli. The TTE was repeated and showed a left ventricular ejection fraction (LVEF) of 40–45%, global hypokinesia, and McConnel Sign, a distinct feature of acute pulmonary embolus; therefore, she was given tissue plasminogen activator (see Supplementary material online, *Videos 2 and 3*). Troponin level suddenly elevated from 103 to 4100 ng/L, so the cardiology team was consulted for the possible acute coronary syndrome. The ECG showed sinus tachycardia with an indeterminate axis and low QRS voltage in precordial leads (*Figure 3*). The emergent coronary angiogram showed non-obstructive coronary artery disease. On the second day, she developed acute kidney injury (creatinine increased from 0.7 to 2.2 mg/dL in 2 days, then 4.8 mg/dL) with metabolic acidosis (pH = 7.1) and persistent hyperkalaemia not responding to medical treatment requiring continuous renal replacement therapy. She became hypotensive, shocked, and was started on vasopressors. The discolouration of the feet was also observed. Her liver enzymes suddenly elevated with alanine transaminase >2000 IU/L and aspartate aminotransferase >8000 IU/L, suggesting a shock-like pattern. The respiratory condition started to deteriorate, became more tachypneic, and required more oxygen that she needed to be intubated with mechanical ventilation. This multi-organ failure occurred during her first 48 h in the MICU. Given the sudden deterioration of the patient's condition in 48 h with multi-system involvement in the setting of her history of APS, the medical team in the MICU considered CAP as the probable diagnosis (more than three systems involved in less than a week with positive antibodies).

Her reports showed increased troponin levels, white blood cells (WBCs), elevated prothrombin time (PT), partial thromboplastin time (PTT) with severe transaminitis. Blood cultures were negative. Liver ultrasonography showed patent hepatic vasculature, so this ruled out portal vein thrombosis. Given that the patient was not improving with very rapid deterioration, the constellation of elevated troponin, WBC, PT, PTT, patent hepatic vasculature, negative infectious workup, lack of schistocytes on peripheral smear, and normal fibrinogen level, diagnosis of the CAPS was concluded. Due to the rapid deterioration and the severity of the condition, the medical team decided to treat immediately without waiting for histopathological confirmation as the patient met the criteria for probable diagnosis. She was started immediately on IV plasmapheresis along with pulse steroids 1 g daily and therapeutic anticoagulation with heparin drip. Within 24 h, the patient showed significant clinical improvement: she defervesced, the discolouration of the right foot improved, and she slowly weaned off pressors. She was eventually extubated and transferred to the floor after 5 days of plasmapheresis therapy. This confirmed the diagnosis of the CAPS after adequate response to the treatment. Bedside echocardiography was repeated after the plasmapheresis course was finished and showed LVEF of 50–55% with resolution of right ventricular function. Unfortunately, no video imaging was stored on our system for this bedside echocardiography, but it was mentioned in the cardiology team notes. She was transitioned to oral prednisone and discharged on the prednisone taper and oral anticoagulation with warfarin. The symptoms resolved during the follow-up appointment; however, no TTE was performed again as the patient was completely asymptomatic. The patient completed the prednisone course and was regularly taking the warfarin for APS.

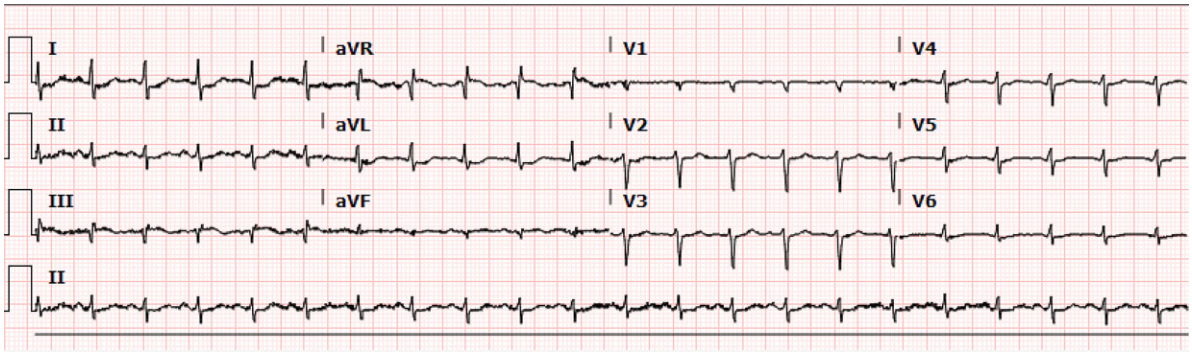


Figure 3 Electrocardiogram showing sinus tachycardia with an indeterminate axis and low QRS voltage in precordial leads.

Table 1 20 Different CAPS cases with cardiovascular complication and the treatments

Author	Case	Treatment
Sukniam *et al.*	A case of CAPS with prosthetic mitral valve thrombosis following mitral valve replacement 2 weeks prior	IVIg, plasmapheresis, methylprednisone
Khizroeva *et al.*	A 24-years-old pregnant female developing CAPS with left bundle branch block and myocardial changes with pulmonary oedema	Fresh-frozen plasma, glucocorticoids, diuretics, anti-aggregants
Hassan *et al.*[15]	A case of CAPS with mitral valve thrombosis	IVIg, plasmapheresis, methylprednisone
Rosenbaum *et al.*	A 48-year-old woman developing CAPS with global myocardial dysfunction and HFrEF	IVIg, plasmapheresis, methylprednisone, Rituximab
El-Dalati *et al.*	CAPS in the setting of mitral valve repair	IVIg, plasma exchange, and corticosteroids
Murtaza *et al.*	A case of CAPS with HFrEF, pericardial effusion and Libman–Sacks endocarditis	Corticosteroids followed by palliative care
Madkaiker *et al.*	CAPS with fluffy ball-like vegetations on the anterior mitral leaflet and aortic cusps	Plasmapheresis and high-dose methylprednisone
Asherson *et al.*	A 56-year-old woman developing CAPS with thrombi in pulmonary arteries	IVIg, plasma exchange with FFP, methylprednisone, IV cyclophosphamide
Asherson *et al.*	A 45-year-old man developing CAPS with acute coronary syndrome	IVIg, plasma exchange with FFP, high-dose pulse steroids
Asherson *et al.*	A 32-year-old man developing CAPS with acute coronary syndrome	Plasma exchange, high-dose intravenous prednisolone
Vieregge *et al.*	CAPS with cardiomyopathy and valvular heart disease	High-dose methylprednisone, plasma exchange, rituximab, cyclophosphamide
Canpolat *et al.*	A 14-year-old girl developing CAPS in the setting of parvovirus B19 infection with HFrEF	IVIg, plasma exchange, and corticosteroids
Tsirpanlis *et al.*	A case of CAPS with myocarditis and reduced ejection fraction	Methylprednisone and plasmapheresis
Ruffati *et al.*	CAPS with circulatory shock and heart failure	IVIg, plasmapheresis, and corticosteroids
Tulai *et al.*	A 46-year-old woman developing CAPS with acute congestive heart failure	IVIg, plasmapheresis, methylprednisone, rituximab
Waisayarat *et al.*	A 12-year-old boy with CAPS and intracardiac thrombus	IVIg, plasmapheresis, methylprednisone
Grinberg *et al.*	A case of CAPS with neovascular glaucoma and Libman–Sacks endocarditis	IVIg, plasmapheresis, corticosteroids
Losonczy *et al.*	A 43-year-old woman developing CAPS with thrombosis in cerebral venous sinuses, aorta, and splenic artery	IVIg, plasmapheresis, corticosteroids
Gupta *et al.*	A 27-year-old woman developing CAPS with cardiogenic shock	IVIg, plasmapheresis, corticosteroids
Akdime *et al.*	A 52-year-old man developing CAPS with HFrEF and left and right ventricular thrombi	IVIg, plasmapheresis, high-dose methylprednisone

Discussion

The pathophysiology of CAPS has been characterized by rapid microvascular thrombosis leading to widespread ischaemic injury. The most prominent theory explains the role of uncontrolled complement activation with an identifiable precipitating event such as infection, surgery, or pregnancy.[5] The data suggest that aPLs activate complement leading to thrombosis in APS. In cardiac involvement in CAPS, mTOR, a kinase integrating various signalling pathways, is activated through molecular markers in coronary vessels' vascular endothelium, leading to valvular lesions and coronary artery disease.[6]

The presenting symptoms of patients with CAPS cover a broad spectrum from persistent fever, cardiac symptoms (heart valve and coronary artery disease), respiratory symptoms (dyspnoea), neurological symptoms, gastrointestinal symptoms, and rashes.[7] Typical clinical findings observed are acute respiratory failure, hypotension, valve lesions, acute kidney injury, transaminitis, and livedo reticularis.[6,7] The classification criteria for CAPS include four main components: three or more organs involved, the rapid development of manifestations within a week, histopathological evidence of small vessel occlusion, and the presence of aPLs.[8] There are some exceptions that still keep CAPS very high on the differential list: involvement of only two-organ systems, no histopathology confirmation, delayed aPLs confirmation, or development of manifestations in more than a week but less than a month.[8] Our patient falls in this probable criteria list, as she had three or more organs involved, symptoms within a week, and was positive for aPLs. However, due to rapid deterioration, we started the therapy before consulting dermatology for the biopsy, so we did not have confirmation through histopathology. The laboratory findings include leucocytosis, aPLs, hypocomplementaemia, elevated cardiac markers including troponin, prolonged blood coagulation markers, high liver enzymes, and thrombocytopenia.[5,9] As mentioned before, common cardiac manifestations include valvular thickening and lesions, coronary artery disease, and myocardial infarction due to microvascular thrombosis. In our patient, myocardial infarction with non-obstructive coronary arteries was still a concern because of the microthrombi that might obstruct the blood vessels. However, the diagnosis of CAPS was made after the heart catheterization was done. Cardiac magnetic resonance imaging could have been ordered to pursue the definitive diagnosis; however, after the diagnosis of CAPS and the patient's response to treatment, no one thought of proceeding with further investigative steps. Common cardiac imaging findings with TTE include decreased right/left ventricular function and elevated left ventricular end-diastolic pressure. The diagnosis of CAPS should be made after excluding other possibilities of portal vein thrombosis, disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathies.

The CAPS has been identified with broad symptoms, with heart involvement being widespread. The heart is affected by direct (autoimmune-mediated), and indirect (thrombosis) mechanisms leading to ischaemic heart disease and left ventricular dysfunction.[4] Hojnik *et al.*[10] reported an extensive echocardiography review that highlighted the significant valve involvement in APS (32–38%) compared with controls (0–5%). On a similar note, a large retrospective analysis indicated that 250 patients with CAPS showed 78% recovery with the combination of glucocorticoids, plasma exchange, and anticoagulation.[11] Another systematic review of 342 patients with CAPS highlights the importance of triple therapy with anticoagulation, glucocorticoids, and either plasma exchange or intravenous immune globulin or both.[12] In the case of patients with CAPS being resistant to triple therapy, several case reports indicate effective treatment of CAPS with Rituximab or Eculizumab.[13,14] Exceptionally, patients with CAPS with heart failure improve with pulse steroids and IV plasmapheresis rather than conventional heart failure treatment. In conclusion, we aimed to report this case to shed light on the management of cardiovascular complications in patients with CAPS and report similarly published cases (*Table 1*).

Lead author biography

I am Nitish Mittal, fourth-year medical student at Texas Tech University Health Sciences Center, Lubbock, TX. I will be heading to UT Houston/McGovern for Internal Medicine residency. I have performed clinic research for the past 4 years and cultivated my knowledge base through different projects, ranging from trans-aortic valve replacement and antiplatelets to multi-system inflammatory syndrome in adults. I have given several oral/poster presentations in various conferences, namely Cardiovascular Research Technologies and New Cardiovascular Horizons. In free time, I enjoy playing tennis/cricket and love spending time with family and friends.

Supplementary material

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

Slide sets: A fully edited slide set detailing these cases and 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: The authors have no financial conflicts to disclose. All authors have reviewed and approved the manuscript, and all authors fulfil the criteria for authorship as mandated by the International Committee of Medical Journal Editors and have no conflict of interest with the submitted data.

Funding: There was no funding required for this case report.

References

1. Lim W. Antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program* 20132013;**2013**:675–680.
2. Radin M, Sciascia S, Bazzan M, Bertero T, Carignola R, Montabone E, Montaruli B, Vaccarino A, Cecchi I, Rubini E, Roccatello D, Baldovino S, Piedmont and Aosta Valley APS Consortium. Antiphospholipid syndrome is still a rare disease-estimated prevalence in the piedmont and Aosta Valley regions of Northwest Italy: comment on the article by Duarte-García et al. *Arthritis Rheumatol* 2020;**72**:1774–1776.
3. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Lakos G, Tincani A, Kontopoulou-Griva I, Galeazzi M, Meroni PL, Derksen RHWM, de Groot PG, Gromnica-Ihle E, Baleva M, Mosca M, Bombardieri S,

Houssiau F, Gris J-C, Quéré I, Hachulla E, Vasconcelos C, Roch B, Fernández-Nebro A, Boffa M-C, Hughes GRV, Ingelmo M. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;**46**:1019–1027.
4. Denas G, Jose SP, Bracco A, Zoppellaro G, Pengo V. Antiphospholipid syndrome and the heart: a case series and literature review. *Autoimmun Rev* 2015;**14**:214–222.
5. Chaturvedi S, Braunstein EM, Yuan X, Yu J, Alexander A, Chen H, Gavriilaki E, Alluri R, Streiff MB, Petri M, Crowther MA, McCrae KR, Brodsky RA. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. *Blood* 2020;**135**:239–251.
6. Canaud G, Bienaimé F, Tabarin F, Bataillon G, Seilhean D, Noël L-H, Dragon-Durey M-A, Snanoudj R, Friedlander G, Halbwachs-Mecarelli L, Legendre C, Terzi F. Inhibition of the mTORC pathway in the antiphospholipid syndrome. *N Eng J Med* 2014;**371**:303–312.
7. Djokovic A, Stojanovich L, Kontic M, Stanisavljevic N, Radovanovic S, Marisavljevic D. Association between cardiac manifestations and antiphospholipid antibody type and level in a cohort of Serbian patients with primary and secondary antiphospholipid syndrome. *Isr Med Assoc J* 2014;**16**:162–167.
8. Asherson R, Cervera R, De Groot P, Erkan D, Boffa M-C, Piette J-C, Khamashta MA, Shoenfeld Y. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**: 530–534.
9. Pontara E, Banzato A, Bison E, Cattini M, Baroni G, Denas G, Calligaro A, Marson P, Tison T, Ruffatti A, Pengo V. Thrombocytopenia in high-risk patients with antiphospholipid syndrome. *J Thromb Haemost* 2018;**16**:529–532.
10. Hojnik M, George J, Ziporen L, Shoenfeld Y. Heart valve involvement (Libman-Sacks endocarditis) in the antiphospholipid syndrome. *Circulation* 1996;**93**:1579–1587.
11. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, Font J, Asherson RA. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. *Arthritis Rheum* 2006;**54**:2568–2576.
12. Cervera R, Rodríguez-Pintó I, G Espinosa on behalf of the Task Force on Catastrophic Antiphospholipid Syndrome. Catastrophic antiphospholipid syndrome: task force report summary. *Lupus* 2014;**23**:1283–1285.
13. Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum* 2012;**64**:2719–2723.
14. Rubenstein E, Arkfeld DG, Metyas S, Shinada S, Ehresmann S, Liebman HA. Rituximab treatment for resistant antiphospholipid syndrome. *J Rheumatol* 2006; **33**:355–357.
15. Hassan MA, Abohelwa M, Elmassry M, Elgwairi E, Whisenant T, Sethi P. Catastrophic antiphospholipid syndrome associated with mitral valve thrombosis. *J Investig Med* 2021.