Received: 7 March 2024 | Revised: 10 May 2024 | Accepted: 25 May 2024

DOI: 10.1002/ccr3.9061

CASE REPORT

Clinical Case Reports Open Access WILEY

Catastrophic antiphospholipid syndrome: challenging case and importance of multidisciplinary evaluation and management

Sharmeen Sorathia[1] | **Aro Daniela Arockiam**[1] | **Elio Haroun**[1] | **Rishabh Khurana**[1] | **Alexandra Hall**[1] | **Meghann McCarthy**[2] | **Rupal K. Shastri**[3] | **Hanny Sawaf**[4] | **Keith R. McCrae**[5] | **Christine L. Jellis**[1] | **Tom Kai Ming Wang**[1]

[1]Section of Cardiovascular Imaging, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA

[2]Section of Vascular Medicine, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA

[3]Department of Rheumatologic and Immunologic Disease, Orthopedic and Rheumatologic Institute, Cleveland Clinic, Cleveland, Ohio, USA

[4]Department of Kidney Medicine, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA

[5]Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence
Tom Kai Ming Wang, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J1-5, Cleveland, OH 44195, USA.
Email: wangt2@ccf.org

Key Clinical Message

Our case depicts a challenging diagnosis of catastrophic antiphospholipid syndrome in a young patient with a heterogenous presentation with extensive clinical course, a wide range of investigations, including multimodality imaging, and multidisciplinary expertise, to initiate prompt treatment addressing multiorgan thrombotic injury.

KEYWORDS

cardiovascular disorders, hematology, nephrology, rheumatology

1 | INTRODUCTION

Catastrophic antiphospholipid syndrome (CAPS) is a rare and aggressive variant of antiphospholipid syndrome (APLS) that occurs in 0.9% of APLS patients.[1] It is characterized by both macrovascular thrombosis and multiorgan involvement of microthrombi within a short duration of time with a high mortality rate of 37%–44%.[2,3] Up until September 2019, the CAPS registry had 547 patients with 571 episodes of CAPS.[4]

2 | CASE HISTORY/EXAMINATION

Here we have a male in his 20s with history of hypertension, morbid obesity, and obstructive sleep apnea, who presented to the emergency department with 3 months of progressively worsening facial and neck swelling, headaches, and dizziness. On physical examination, the patient had tachycardia with a heart rate of 102 bpm, other vital signs normal, and diffuse facial swelling.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT)

CT scan revealed thrombus in the superior vena cava (SVC) extending to the left brachiocephalic vein with extensive collaterals (Figure 1A–D), while laboratory work showed triple-positive APLS along with additional investigations mentioned in Table 1. He was initiated on low molecular weight heparin, and then bridged and transitioned to warfarin.

Two months later the patient presented to an outside hospital with chest discomfort, dull bilateral flank pain, and diarrhea without preceding viral illness. The physical examination was unremarkable with normal vital signs. His electrocardiogram showed mild ST elevation in the inferior and lateral leads. Initial laboratory tests showed serially elevated high sensitivity troponin levels. Given presentation of acute myocardial infarction/injury, left heart catheterization was performed, and no coronary artery disease was seen (Figure 2). Additional investigations including autoimmune workup were performed, summarized in Table 1. CT abdomen and pelvis with contrast showed subtle infrarenal abdominal aortic wall thickening and adjacent stranding which was suspicious for aortitis/vasculitis (Figure 1F,G). Echocardiogram (ECG) showed normal biventricular systolic function, with no pericardial effusion. The patient was started on colchicine 0.6 mg twice daily for concern of myopericarditis. A renal biopsy was recommended due to the presence of proteinuria and concern for vasculitis, which he preferred to discuss further as an outpatient.

Three days later, he re-presented to the emergency department with recurrence of chest pain radiating to the back which did not improve with colchicine. He was hemodynamically stable. He was transferred to our hospital. Laboratory results were notable for elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) and creatinine, along with decreased platelet level. Urine studies showed mild 1+ hematuria, persistent 3+ proteinuria and a urine protein to creatinine ratio of 0.95. The electrocardiogram was unremarkable. His SARS-CoV-2 test was negative on this and prior admissions. CT chest, abdomen, and pelvis was again suggestive of aortitis and persistent SVC syndrome. Echocardiography did not show any ventricular dysfunction or pericardial effusion. Renal ultrasound was also unremarkable. A cardiac magnetic resonance imaging (MRI) was then performed which showed mid-myocardial and subendocardial late gadolinium enhancement (LGE) of the basal inferior, mid lateral, mid inferior, apical inferior, apical medial, and apical lateral wall, with otherwise low-normal left ventricular systolic function (ejection fraction 51%), overall suspicious for multivessel coronary embolic infarcts or myocarditis (Figure 3).

The patient was on heparin infusion for anticoagulation in hospital, however over the next several days, the patient's renal function and thrombocytopenia worsened, although anti-PF4 levels were negative, suggesting that heparin induced thrombocytopenia was unlikely, and workup for disseminated intravascular coagulation was

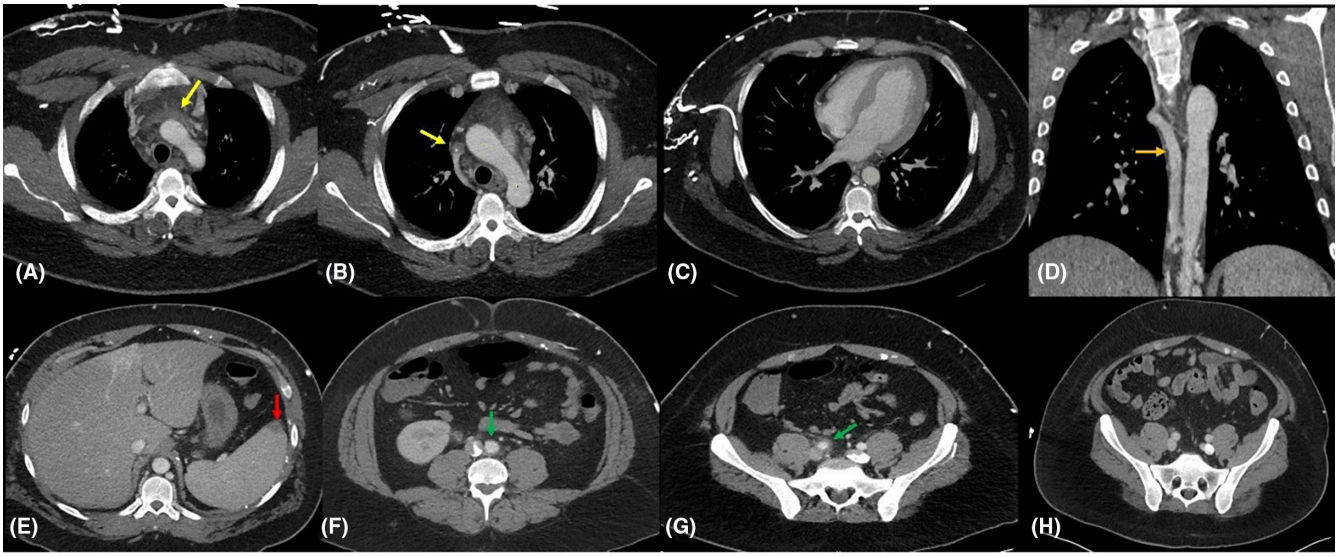

FIGURE 1 Computed tomography angiography (CTA; axials and reformatted coronal) images showing hypodense filling defect (yellow arrows, A, B) in superior vena cava and left brachiocephalic vein suggesting thrombus; chest wall collaterals are noted (A–C) and azygous vein is prominent (orange arrow, D). Wedge-shaped hypodensity is noted in spleen suggesting infarct (red arrow, E). Subtle wall thickening and adjacent stranding is seen around infrarenal abdominal aorta and right common iliac artery suggesting aortitis (green arrows, F, G). Resolution of previously seen mural thickening and fat stranding is appreciated on follow-up CTA (H).

TABLE 1 Summary of key patient investigation results.

Laboratory investigation	Initial presentation	Second hospitalization	Third hospitalization	Normal values/ range	Details/comments
Anti-cardiolipin IgM	65.1 MPL			<12.5 MPL	High
Anti-cardiolipin IgG	64.6 GPL			<15.0 GPL	High
Beta-2 glycoprotein IgM	67 SMU			<20 SMU	High
Beta-2 glycoprotein IgG	37 SGU			<20 SGU	High
Lupus anticoagulant	Positive			Negative	A positive screening test, mixing study, and phospholipid dependence and exclusion of other coagulopathies or inhibitors
Anti-nuclear antibodies (ANA)	Positive (titer 1:160)	Negative		Negative	Nuclear fine speckled pattern
Protein, urine random	97 mg/dL			0–20 mg/dL	High
Protein/creatinine ratio	1.17 mg/mg	1.22 mg/mg		<0.15 mg/mg	High
Serum creatinine	0.92 mg/dL	0.86 mg/dL	1.36 mg/dL	0.73–1.22 mg/dL	High in third hospitalization
White blood cell count		16.5 k/uL		3.70–11.00 k/uL	High
Hemoglobin	11.5 g/dL	12.5 g/dL	13 g/dL	13.0–17.0 g/dL	Initially low
Platelets	134 k/uL	201 k/uL	108 k/uL to lowest of 56 k/uL	150–400 k/uL	Worsening thrombocytopenia in the third hospitalization
High sensitivity troponin		430 ng/L 1479 ng/L	1084 ng/L	<12 ng/L	High
N-terminal pro b-type natriuretic peptide (NTPBNP)		414 pg/mL	3186 pg/mL	<125 pg/mL	High
C-reactive protein		5.5 mg/dL	2.9 mg/dL	<0.9 mg/dL	High
Westergren sedimentation rate	102 mm first hour	106 mm first hour	114 mm/h	0–15 mm first hour	High
Serum kappa free		52.4 mg/L		3.3–19.4 mg/L	High
Serum lambda free		25.9		5.7–26.3 mg/L	Normal
Serum Kappa/lambda		2.02		0.26–1.65	High
Antibody for coxsackie B type 1		≥1:640		<1:10	High
Immunoglobulin A		337 mg/dL		70–400 mg/dL	Normal
Immunoglobulin D		7.2 mg/dL		≤15.3 mg/dL	Normal
Immunoglobulin E		603 kU/L		<114.0 kU/L	Normal
Immunoglobulin M		133 mg/dL		40–230 mg/dL	Normal
Complement 3	134 mg/dL	166 mg/dL		86–166 mg/dL	Normal
Complement 4	14 mg/dL	24 mg/dL		13–46 mg/dL	Normal

(Continues)

TABLE 1 (Continued)

Laboratory investigation	Initial presentation	Second hospitalization	Third hospitalization	Normal values/ range	Details/comments
TSH	2.600 mIU/L			0.270–4.200 mIU/L	Normal
Syphilis rapid plasma reagin		Non-reactive		Non-reactive	Normal
Antinuclear cytoplasmic antibodies (ANCA)		Negative		Negative	Normal
Hepatitis B core antibody	Negative			Negative	Normal
Anti-DS-DNA antibody		<12 IU/mL		<30 IU/mL	Normal
Anti-smith antibodies		Negative		Negative	Normal
Haptoglobin	121 mg/dL		223 mg/dL	31–238 mg/dL	Normal
Lactate dehydrogenase	444 U/L		352 U/L	135–225 U/L	High
Coombs direct	Positive		Positive	Negative	Positive
Absolute reticulocytes	0.110			0.018–0.100 M/uL	High
PNH granulocyte clone	<0.01		<0.01	<0.01%	Normal
PNH RBC clone sum			1.77%	<0.01%	High
PNH RBC clone-partial Ag loss (type II)			1.53%		High
PNH RBC clone-partial Ag loss (type III)	0.08%		0.24%	<0.01%	Rising in the third hospitalization

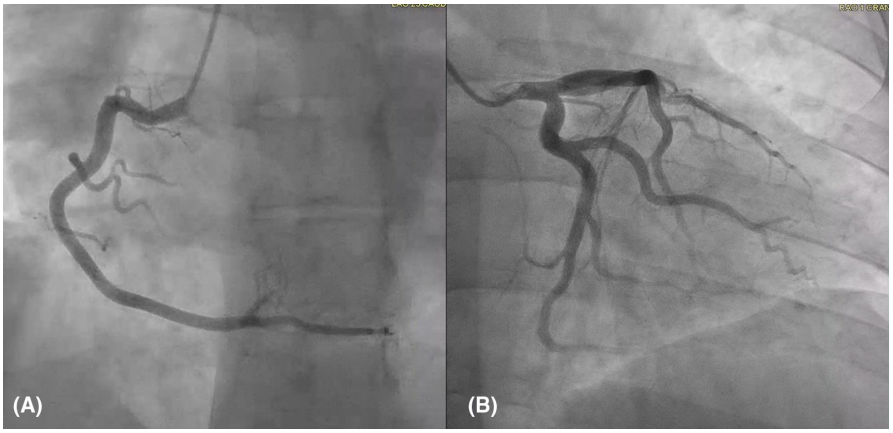

FIGURE 2 Coronary angiography images revealing normal coronaries. (A) Right coronary artery view, (B) Left coronary artery view.

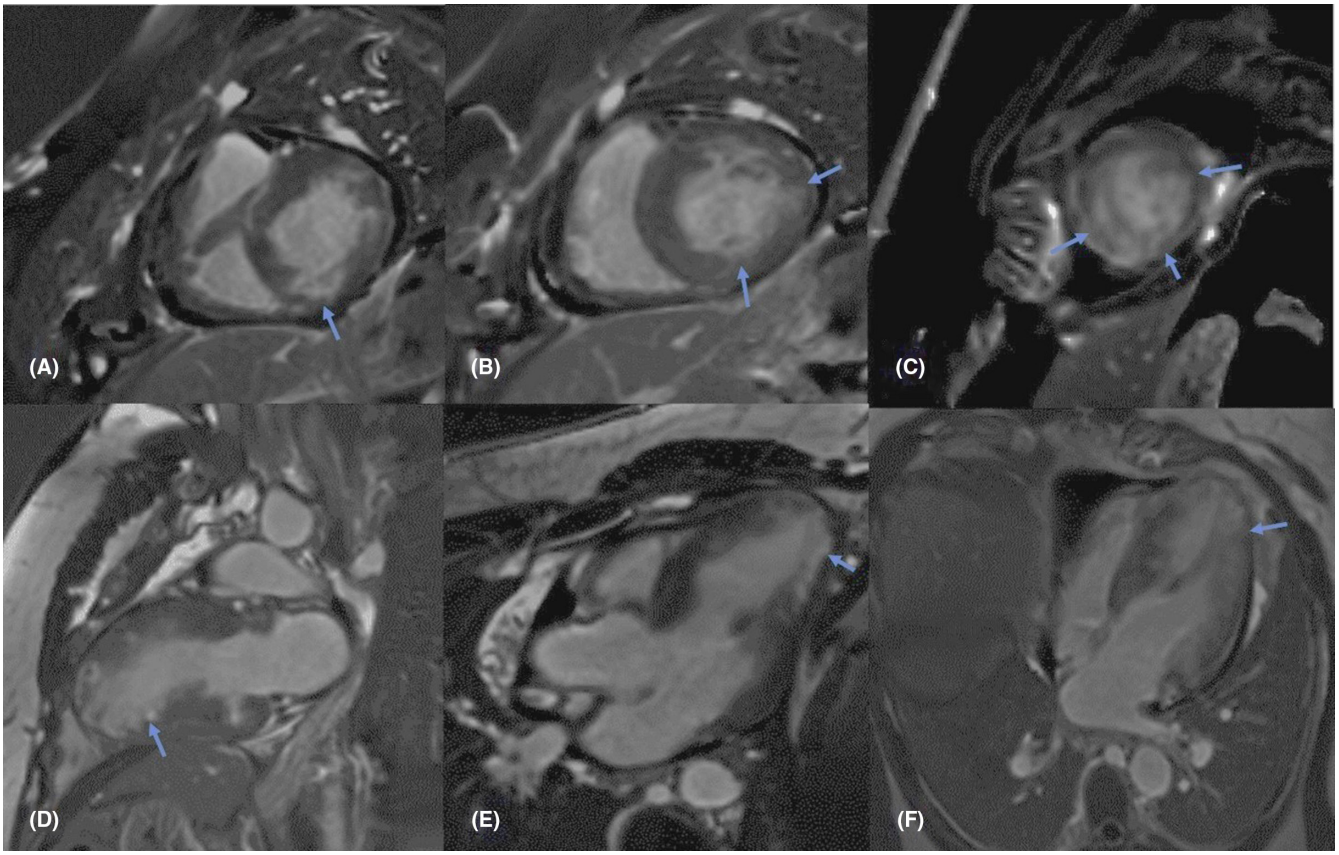

FIGURE 3 Delayed gadolinium enhancement magnetic resonance imaging in short axis (basal-mid-apical LV segments; (A–C) and 2-chamber (D), 3-chamber (E) and 4-chamber (F) revealing mid-myocardial and subendocardial late gadolinium enhancement of the basal inferior, mid lateral, mid inferior, apical inferior, apical medial, and apical lateral wall, representing multiple coronary territories, suspicious for multivessel coronary embolic infarcts or myocarditis.

also unremarkable. Despite a positive direct coombs test and elevated lactate dehydrogenase, hemolysis seemed unlikely given normal haptoglobin and absence of schistocytes. He was also noted to have modestly rising paroxysmal nocturnal hemoglobinuria (PNH) clone; however, as granulocytes were not affected and the clones were a very small percentage, it was deemed unlikely to be clinically significant. For a planned kidney biopsy, anticoagulation was held; however, 2 h later, the patient complained of severe, sudden onset abdominal pain. A CTA showed a new wedge-shaped hypoattenuation in the anterior spleen concerning for a developing infarct; so intravenous heparin was restarted and continued for the rest of the admission (Figure 1E). The renal biopsy was subsequently deferred due to risk of further embolic phenomena. Due to the simultaneous involvement of more than three organs (heart, SVC, kidneys, and spleen) within a short timeframe, a diagnosis of presumptive CAPS was made.

The patient received IV methylprednisolone 1 g daily for 3 days, followed by rituximab and oral prednisone, and underwent four sessions of plasma exchange.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW UP)

Following treatment, the patient's renal function improved (creatinine decreased from 4.21 to 2.21 mg/dL by discharge) and thrombocytopenia resolved. Ultimately, he was discharged on Day 20 of this hospitalization with an oral prednisone taper (starting with 70 mg daily), rituximab 375 mg/m^2 weekly for a total of 4 doses, and intravenous heparin infusion bridging to warfarin. He had no recurrent chest pain thereafter. One week later, a repeat CT imaging showed decreased stranding and inflammation around the infrarenal aorta (Figure 1H). His last creatinine value was 1.37 mg/dL and platelets 321 k/uL. At subsequent outpatient follow-up, about 5 months after his initial presentation, he felt overall improved.

5 | DISCUSSION

We present the case of a young patient hospitalized with CAPS, with a focus on the challenging clinical diagnostic course and prompt treatment. CAPS involves rapidly progressive and extensive thromboembolic phenomenon as seen in our challenging case. Half of patients presenting with CAPS have no prior history of APLS.[4] CAPS is diagnosed when the following criteria are met: involvement of three or more organs develops simultaneously or within 1 week; presence of APLS antibodies is confirmed; and histopathological evidence of small vessel occlusion in at least one organ is found. Probable CAPS is defined as having some but not all of the criteria met.[5] Two thirds of patients can have an identifiable trigger which can include infections, surgery, or malignancies. In our case, possible coxsackie B viral infection may have been a potential precipitant. Most commonly affected organs include the kidneys (73%), lungs (60%), brain (56%), heart (50%), and skin (47%).[3] Our patient was first found to have SVC thrombosis, then 2 months later was re-admitted with acute myocardial injury, acute kidney injury, and splenic infarcts occurring sequentially within 1 week.

The cardiac manifestation of our case warrants further discussion. During the second hospitalization, he exhibited acute myocardial injury (chest pain, abnormal ECG, and elevated troponins) with normal coronary arteries. This prompted suspicion for peri-myocarditis. However, subsequent cardiac MRI revealed late LGE pattern affecting multiple vascular territories as seen in other cases.[6–8] Both multivessel coronary embolic infarcts and myocarditis are plausible.[9] Indeed, we suspect both to be present, and cardiac MRI plays an important role when cardiac involvement is suspected. Other cardiac manifestations in CAPS can involve valvular thrombosis, nonbacterial thrombotic endocarditis, intracardiac thrombus, micro- and macrovascular myocardial infarct, and systolic dysfunction.[10] After cerebral involvement, cardiac effects of CAPS are noted to be the second most frequent cause of death.[11] Clinical deterioration has been seen in the form of worsening systolic dysfunction,[7,8,10,12,13] cardiogenic shock,[7,14] cardiac arrest,[12] and need for mechanical support.[12,14]

Several important manifestations in our case leading to CAPS diagnosis were acute kidney injury, thrombocytopenia, and multifocal coronary artery involvement. The differential diagnoses were broadened to other autoimmune conditions such as systemic Lupus erythematosus and associated disorders, Takayasu's arteritis, or other vasculitis. Target organ biopsy (renal in our case) showing ischemic microvascular injury of the kidneys, myocardium, or skin, as described previously, might have provided valuable insight into the underlying diagnosis.[6,12,14,15] However, the risks of withholding anticoagulation for biopsy after development of a splenic infarct was deemed too great. While large vessel vasculitis was considered, given the finding of aortitis, involvement of the glomerulus made this less likely. Of note, aortitis is a rare finding in CAPS, with only two cases having previously been reported in the literature.[16] Nevertheless, few APLS patients would've undergone extensive whole-body imaging like our case did to identify aortitis, which itself is often a manifestation or autoimmune and rheumatological condition so is likely associated with CAPS in our case. After thorough multidisciplinary case review, consensus was that CAPS was the most likely unifying diagnosis.

In a 2018 clinical practice guidelines specific to CAPS, the only strong recommendation was the use of therapeutic anticoagulation with unfractionated heparin, while effectiveness of direct oral anticoagulants is unknown.[17] Patients diagnosed with CAPS have been successfully treated with IV pulse steroids,[7,12,15] intravenous immunoglobulin (IVIG),[7,8,12,15] anticoagulation, and plasma exchange,[13–15] with improvement in the function of the organs involved. Patients have also received emerging therapies including rituximab,[7,13–15] cyclophosphamide,[7,8] and eculizumab.[12,18] In a descriptive analysis of patients in the CAPS registry, combined treatment with anticoagulation, steroids, plasma exchange, and/or IVIG was associated with achievement of higher recovery rates.[2] A combination of glucocorticoid, heparin, and either plasmapheresis

or IVIG was recommended over the use of single-agent therapies or other combinations. Although plasmapheresis has been performed in most studied patients, there is insufficient evidence to compare it with IVIG as first-line treatment. IVIG is suggested in patients with immune thrombocytopenia, and avoided in elderly and patients with renal impairment, while plasmapheresis should be considered in the presence of microangiopathic hemolytic anemia. For rituximab, a prior study found that it may be effective in managing non-criteria manifestations of APLS whilst being a safe treatment option, and our multidisciplinary team based on this and prior limited experience in treating associated conditions decide to proceed with including rituximab in treating this patient.[19]

Our case illustrates the challenges in the diagnosis of CAPS. Multimodality imaging and a wide range of laboratory tests, together with integrative expertise from a multidisciplinary team, were necessary to arrive at the diagnosis, and initiate appropriate therapies. Prompt treatment with both anticoagulation and immunosuppressive therapy is necessary to appropriately address multiorgan injury in patients with CAPS.

AUTHOR CONTRIBUTIONS

Sharmeen Sorathia: Writing – original draft. **Aro Daniela Arockiam:** Writing – original draft. **Elio Haroun:** Writing – original draft. **Rishabh Khurana:** Visualization; writing – original draft. **Alexandra Hall:** Conceptualization; writing – review and editing. **Meghann McCarthy:** Conceptualization; writing – review and editing. **Rupal K. Shastri:** Conceptualization; writing – review and editing. **Hanny Sawaf:** Conceptualization; writing – review and editing. **Keith R. McCrae:** Conceptualization; writing – review and editing. **Christine L. Jellis:** Conceptualization; writing – review and editing. **Tom Kai Ming Wang:** Conceptualization; supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest for all authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Sharmeen Sorathia https://orcid.org/0009-0004-2109-7806

REFERENCES

1. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10 year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis*. 2015;74(6):1011-1018. doi:10.1136/annrheumdis-2013-204838
2. Cervera R, Bucciarelli S, Plasín MA, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the CAPS Registry. *J Autoimmun*. 2009;32(3–4):240-245. doi:10.1016/j.jaut.2009.02.008
3. Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the international CAPS registry. *Autoimmun Rev*. 2016;15(12):1120-1124. doi:10.1016/j.autrev.2016.09.010
4. Cervera R, Rodríguez-Pintó I, Legault K, Erkan D. 16th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. *Lupus*. 2020;29(12):1594-1600. doi:10.1177/0961203320951260
5. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. *Autoimmun Rev*. 2010;10(2):74-79. doi:10.1016/j.autrev.2010.08.005
6. Azoulay LD, Pineton de Chambrun M, Larcher R, et al. Prevalence, characteristics and outcome of cardiac manifestations in critically-ill antiphospholipid syndrome patients. *J Autoimmun*. 2022;133:133. doi:10.1016/j.jaut.2022.102908
7. Rosenbaum AN, Anavekar NS, Ernste FC, et al. A case of catastrophic antiphospholipid syndrome: first report with advanced cardiac imaging using MRI. *Lupus*. 2015;24(12):1338-1341. doi:10.1177/0961203315587960
8. Plastiras SC, Tzelepis GE, Kelekis NL, Vlachoyiannopoulos PG. Catastrophic antiphospholipid syndrome with heart involvement: diagnostic utility of the cardiac MRI. *Int J Cardiol*. 2007;116(1):e29-e31. doi:10.1016/j.ijcard.2006.08.083
9. Girish B, Gainder S, Saha SC, Krishnappa D. Rare presentation of catastrophic antiphospholipid syndrome with myocarditis in post-partum period: case report and review of literature. *J Obstet Gynecol India*. 2018;68(1):70-72. doi:10.1007/s13224-017-0974-7
10. Mittal N, Abohelwa M, Rahman MR, Shurmur S. Cardiovascular complications of catastrophic antiphospholipid syndrome: a case report and review of literature. *Eur Heart J Case Rep*. 2022;6(5):1-6. doi:10.1093/ehjcr/ytac199
11. Bucciarelli S, Espinosa G, Cervera R, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. *Arthritis Rheum*. 2006;54(8):2568-2576. doi:10.1002/art.22018
12. Lai AC, Feinman J, Oates C, Parikh A. A case report of acute heart failure and cardiogenic shock caused by catastrophic antiphospholipid syndrome and lupus myocarditis. *Eur Heart J Case Rep*. 2022;6(12):1-5. doi:10.1093/ehjcr/ytac446
13. Elmusa E, Raza MW, Muneeb A, Zahoor H, Naddaf N. Catastrophic antiphospholipid syndrome: a rare cause of acute heart failure. *Cureus*. 2023;15:e42012. doi:10.7759/cureus.42012
14. Hucker WJ, Chatzizisis YS, Steigner ML, Winters GL, Kirshenbaum JM. Myocardial catastrophe a case of sudden, severe myocardial dysfunction. *Circulation*. 2014;130(10):854-862. doi:10.1161/CIRCULATIONAHA.113.007417
15. Tulai IM, Penciu OM, Raut R, Rudinskaya A. Catastrophic antiphospholipid syndrome: presenting as congestive heart failure

in a patient with thrombotic microangiopathy. *Tex Heart Inst J*. 2019;46(1):48-52. doi:10.14503/THIJ-17-6472

16. Escoda T, George J, Jarrot PA, et al. Aortitis is an under-recognized manifestation of antiphospholipid syndrome: a case report and literature review. *Lupus*. 2022;31(6):744-753. doi:10.1177/09612033221091142
17. Legault K, Schunemann H, Hillis C, et al. McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. *J Thromb Haemost*. 2018;16(8):1656-1664. doi:10.1111/jth.14192
18. López-Benjume B, Rodríguez-Pintó I, Amigo MC, et al. Eculizumab use in catastrophic antiphospholipid syndrome (CAPS): descriptive analysis from the CAPS Registry. *Autoimmun Rev*. 2022;21(4):1-8. doi:10.1016/j.autrev.2022.103055
19. Erkan D, Vega J, Ramón G, Kozora E, Lockshin MD. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum*. 2013;65(2):464-471. doi:10.1002/art.37759

How to cite this article: Sorathia S, Arockiam AD, Haroun E, et al. Catastrophic antiphospholipid syndrome: challenging case and importance of multidisciplinary evaluation and management. *Clin Case Rep*. 2024;12:e9061. doi:10.1002/ccr3.9061