Catastrophic antiphospholipid antibody syndrome as a first manifestation of primary antiphospholipid antibody syndrome in a middle-aged man

Nazrul Hassan Jafry¹ · Muhammed Mubarak² · Ejaz Ahmed¹ · Fazal Akhtar¹

Received: 11 October 2019 / Accepted: 7 January 2020 / Published online: 27 January 2020
© Japanese Society of Nephrology 2020

Abstract

Catastrophic antiphospholipid antibody syndrome (CAPS) is a severe form of antiphospholipid antibody syndrome (APS) that sometimes represents the first manifestation of the later syndrome. The clinical manifestations of CAPS are relatively non-specific. Hence, the diagnosis may be delayed, resulting in high mortality. We herein present a case of a 40-year-old male who presented with rapid-onset renal failure, gangrene of finger and toe tips and hematological abnormalities with no underlying secondary cause for this complication. The symptoms were precipitated by febrile illness of short duration. A provisional diagnosis of CAPS was made and treatment instituted. With timely diagnosis and intervention, both the life of the patient and kidney function were salvaged. A high index of suspicion for CAPS is important as early treatment can be lifesaving.

Keywords Antiphospholipid antibodies · CAPS · Gangrene · Renal failure

Introduction

Catastrophic antiphospholipid antibody syndrome (CAPS) is the severe form of antiphospholipid antibody syndrome (APS) that sometimes represents the first manifestation of the later syndrome. Encountered in less than 1% of patients with APS, CAPS is characterized by accelerated and widespread small/medium vessel thromboses with multiple organ involvement and a mortality of nearly 50% despite aggressive multimodal intensive treatment. The clinical manifestations are relatively non-specific. Hence, its accurate diagnosis may be delayed, resulting in high mortality [1–3]. A high index of suspicion for CAPS is important as early treatment can be lifesaving. An international consensus statement on preliminary criteria for the diagnosis of CAPS has been published to provide a uniform diagnostic approach to patients with CAPS [4–6]. The correct diagnosis of CAPS may be

challenging, as it shares clinical features with other life-threatening conditions such as sepsis, disseminated intravascular coagulation, heparin-induced thrombocytopenia, or other thrombotic microangiopathies [thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and HELLP syndrome (hemolytic anemia, elevated liver enzymes, low platelet count)]. Nonetheless, early recognition of CAPS is crucial; as soon as the diagnosis is suspected, patients should receive anticoagulation and corticosteroids (first-line therapies), with the addition of plasma exchange or intravenous immunoglobulin (IVIG) (second-line therapies) in the presence of poor prognostic factors and/or lack of response. In the case of deteriorating clinical situation, a third-line treatment (such as cyclophosphamide or rituximab) is recommended [1, 3, 7–9].

We herein present a case of a 40-year old male who presented with CAPS with no underlying secondary cause for this complication. With timely diagnosis and intervention, his kidney function and life were saved.

✉ Nazrul Hassan Jafry
dr_nazar_jafferi@yahoo.com

¹ Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi 74200, Pakistan

² Department of Pathology, Sindh Institute of Urology and Transplantation (SIUT), Karachi 74200, Pakistan

Case report

A 40-year-old male, farmer, with no known co-morbidities, presented with the complaints of fever for 7 days and blackish discoloration of both hands and feet for 5 days. The fever was high grade, sudden in onset, associated with chills and rigors, and temporarily relieved by taking oral paracetamol. He had two episodes of watery, non-projectile vomiting, not associated with abdominal pain and three episodes of loose stools, soft in consistency, non-mucoid, non-bloody in nature, and self-resolving. Fever lasted for 2 days. After subsidence of fever, he developed blackish discoloration of fingers of both hands and feet and tip of the nose associated with mild non-progressive pain (Fig. 1a, b). Simultaneously, he developed bilateral leg swelling. There was no bleeding from any site, cough, shortness of breath, arthralgia, photosensitivity, hair loss, mouth ulcers, hematuria, or cola-colored urine. He was admitted in a district headquarter hospital, where after detection of raised urea and creatinine, he was referred to our center for further evaluation and management.

On detailed history taking, no significant past medical and surgical history was elicited. No history of blood transfusion was given. Drug history including allergy to drugs was not significant. There was no family history of diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), tuberculosis (TB) or renal disease. Socioeconomically, he belonged to a poor class family.

On general physical examination, he was a middle aged, ill-looking male of normal height and built, not in acute distress with following vitals: Blood pressure (BP) of 129/73 mmHg, pulse of 90 beats/min, temperature of 98.6 °F, and respiratory rate of 18 breaths/min. Pallor was present, but jaundice, clubbing, cyanosis, and dehydration were absent. Pedal edema was present extending upto the knees, and pitting in nature. Jugular venous pressure was not raised. Thyroid was not enlarged and lymph nodes were not palpable. His systemic examination was unremarkable.

On hematological investigations, hemoglobin (Hb) was 6.4 g/dl, mean corpuscular volume (MCV), 51.2 fl, mean corpuscular hemoglobin (MCH), 15.5 pg, mean corpuscular hemoglobin concentration (MCHC), 30.2 g/dl, total leukocyte count (TLC), $27.7 \times 10^9/l$, and the differential showed neutrophils, 84%, and lymphocytes, 10%. The platelet count was $29 \times 10^9/l$. On peripheral film, there was anisocytosis, hypochromia, microcytosis, and poikilocytosis. No schistocytes were seen. Malarial parasites (MP) were not seen.

Biochemical investigations showed serum urea of 324 mg/dl, creatinine 11.16 mg/dl, sodium 130 mEq/l, potassium 5.0 mEq/l, chloride 105 mEq/l, and bicarbonate 16.0 mEq/l. Total bilirubin was 3.2 mg/dl, direct bilirubin 1.7 mg/dl, alkaline phosphatase 166 μ l, serum glutamic oxaloacetic transaminase (SGOT) 135 U/l, serum glutamic pyruvic transaminase (SGPT) 190 U/l, gamma-glutamyl-transferase (GGT) 51 U/l and lactate dehydrogenase (LDH) was 1149 U/l. Prothrombin time (PT) was 15.4 s (control 10.5 s), activated partial thromboplastin time (APTT) was 32.9 s (control 25.8 s), and international normalized ratio (INR) was 1.47 (normal 0.9–1.2).

Urine examination showed pH of 6.5 and specific gravity of 1.010. Urinary albumin was 2+, sugar was nil, red blood cells (RBCs) were numerous and pus cells, also numerous. No casts were seen.

Chest X-ray was normal. Ultrasound whole abdomen showed liver span of 15.0 cm, with altered texture with regular margins. No space occupying lesion, and no ductal dilatation was noted. Portal vein was 0.9 cm. Spleen was enlarged (13.6 cm). No hilar varices was seen. There was mild ascites. Both kidneys were normal in size and echogenic, but no hydronephrosis, or calculi were seen.

Arterial Doppler of both upper and lower limbs including brachial, radial, and ulnar arteries of both upper limbs and femoral, anterior tibial, posterior tibial, and dorsalis pedis of both lower limbs showed normal triphasic flow and wave pattern on color Doppler imaging. There was also normal flow in renal arteries and veins.

Fig. 1 **a** Clinical photograph of the patient showing digital gangrene and imminent gangrene of the tip of nose. **b** Developing gangrene of feet and toes

Echocardiography showed dilated left atrium, and high-normal left ventricular size. Ejection fraction was 78%. There was grade II diastolic dysfunction.

Patient remained afebrile during his hospital stay. He was empirically treated with intravenous (IV) antibiotics, piperacillin/tazobactam. Both urine and blood cultures turned out to be negative.

His hematological parameters improved over the course of his hospital admission, as shown in Table 1.

On serological investigations, hepatitis B surface antigen (HBsAg) was negative, while anti-hepatitis C virus (HCV) was positive. Human immunodeficiency virus (HIV) was negative. C3 was 0.85 g/l (normal 0.79–1.52 g/l) and C4: 0.10 g/l (normal 0.16–0.38 g/l). Antinuclear antibody (ANA) was negative, antistreptolysin O titer (ASOT) was 204 IU/ml, and rheumatoid factor (RF) was 85 IU/ml. Both cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were negative. The lupus anticoagulant (LA) was 1.33 (normal 0.8–1.2), protein C total was 43% (reference range 70–150%), protein S ac was 59% (reference range 60–130%), antithrombin III was 51%, (reference range 74–125%) and activated protein C resistance (APCR) was 6.53, (ratio range > 2 (negative) 1.3–1.8 (heterozygous) and 0.9–1.1 (homozygous)).

HCV RNA was positive and genotype was 3a. The serum sample tested positive for cryocrit; however, it was < 1%.

On further serological investigation for antiphospholipid antibodies (APLA), antiphospholipid β 2-gp1 screen was positive. On specific isotype analysis, IgM was positive (104.35 SM units), IgG was negative (< 9.4 SG units) and IgA was positive (133.65 SA units). Anticardiolipin antibody screen was weakly positive. On isotype analysis, IgG weakly positive (16.47 GPL U/ml), IgM was negative (9.95 MPL U/ml) and IgA was negative (< 9.4 APL U/ml). Repeat thrombophilia profile revealed lupus anticoagulant to be 1.12 (reference range 0.8–1.2), protein C total was 75% (reference range 70–150%), protein S ac was 73% (reference range 60–130%), antithrombin III was 80% (reference range 74–125%), and activated protein C resistance (APCR) was 5.65 [ratio range > 2 (negative) 1.3–1.8 (heterozygous) 0.9–1.1 (homozygous)]. D-dimer values were within normal range. ADAMTS assay was not done due to non-availability of the test at that time.

Renal biopsy was performed, which showed an adequate biopsy with upto 19 glomeruli. Of these, four were almost globally sclerosed, five showed acute ischemic changes, and two showed segmental to global collapse of capillary tufts with

associated podocyte hypertrophy and hyperplasia, as shown in Fig. 2. The main lesion was found in the arterioles, which showed intimal proliferation with marked luminal narrowing and extravasation of RBCs into the wall, suggestive of thrombotic microangiopathy of some duration (Fig. 2a–d). An occasional glomerulus also showed evidence of endocapillary hypercellularity, likely representing endothelial cell proliferation with focal double contouring of some of the capillary walls. One glomerulus also showed evidence of mesangiolysis with aneurysmal dilation of some capillary loops (Fig. 3). There was patchy moderate to severe interstitial inflammation and acute tubular injury. A working diagnosis of probable CAPS was made and treatment was started as soon as his platelet count started improving.

He was treated aggressively using multimodal therapy with renal replacement therapy (RRT), anticoagulation, and plasmapheresis. For anticoagulation, he was given Inj. Clexane (Enoxaparin) 1 mg/kg, daily, along with low-dose warfarin (2.5–5 mg, daily) with daily monitoring of INR with target INR of 2–2.5 for 2 weeks. Fourteen sessions of plasmapheresis were done. His platelet count and coagulation profile normalized 10 days after admission. He was last hemodialysed on 13/12/16 followed by removal of his double lumen catheter. His urinary output started improving with a decreasing trend in serum creatinine as shown in Table 2.

The patient's digits showed nearly complete healing (Fig. 4). The patient was advised regular follow-up and his APLA titers were positive with more or less same titers at 12 weeks of follow-up, thus corroborating the definitive diagnosis of CAPS according to Sydney revised Sapporo criteria of APS. He was referred to liver clinic for further evaluation and management of HCV infection.

Discussion

CAPS is a rare life-threatening complication of APS, characterized by fulminant onset of widespread intravascular thrombosis that results in multi-organ ischemia and failure [1–5]. It complicates around 1% of cases of APS. Most of the time, it complicates known cases of APS. However, it can sometimes manifest as the first presentation of APS, as in our case. A prior history of APS is of great help in making a correct diagnosis [6–11].

Table 1 Hematological parameters of the patient during hospital stay

	21/11/16	22/11/16	23/11/16	24/11/16	25/11/16
Hemoglobin (g/dl)	7.2	7.9	8.1	7.4	7.6
Total leucocyte count ($\times 10^9$ /l)	24.8	22.0	22.3	20.1	18.6
Platelets ($\times 10^9$ /l)	36	32	41	46	66

Fig. 2 **a** Low-power photomicrograph showing many solid appearing glomeruli and significant parenchymal damage (JMS, $\times 40$). **b** Medium-power view showing two globally sclerosed glomeruli and one blood-less, ischemic glomerulus (HE, $\times 100$). **c** Same glo-

meruli as in **B** on PAS stain (PAS, $\times 100$). **d** One arteriole showing marked endothelial proliferation with severe narrowing of the lumen (HE, $\times 200$)

Fig. 3 **a** Low-power photomicrograph showing dissolution of mesangial matrix in the glomerulus in the lower field with mild aneurysmal dilation of the capillary loops (arrows). Mesangial matrix is very scanty in this glomerulus. (JMS, $\times 200$). **b** High-power photomicrograph showing endocapillary hypercellularity with thick capillary

walls and markedly narrowed capillary lumina. A few capillary walls show double contouring appearance (arrows). An adjacent arteriole is showing marked intimal proliferation with severe narrowing of the lumen and red cell extravasation in the wall. (JMS, $\times 400$)

Table 2 Trend of renal functions during later period of hospital admission

	14/12/16	15/12/16	16/12/16	17/12/16	18/12/16	19/12/16	20/12/16
Urea (mg/dl)	94	124	132	127	137	133	138
Creatinine (mg/dl)	5.42	4.86	4.74	4.84	4.49	4.35	3.63

Fig. 4 **a** Photograph of the hands of patient showing recovery from the gangrene. **b** The feet and toes also show near complete recovery

CAPS is characterized by intravascular thrombosis affecting predominantly the microcirculation. However, it can involve the larger vessels such as arteries, veins or both. Its clinical presentation is highly variable, hence the difficulty in making diagnosis. Its diagnosis requires both clinical and laboratory criteria [3, 4]. If all four criteria are met, the diagnosis is definite and if less, then the diagnosis is probable. A high index of suspicion should be kept for an early diagnosis of this condition. Early diagnosis and effective treatment can save the life of the patient [4, 5]. Our case fulfilled all the criteria of the diagnosis of the syndrome and the complications developed within one week period after subsidence of fever, thus fulfilling the time obligations of the definition. We started anticoagulant treatment and plasmapheresis as soon as we thought of this diagnosis and did not wait for all the test results. Otherwise, this could have resulted in progression of the disease, with involvement of other organ systems and potentially death of the patient. Our patient developed ischemic lesions affecting the skin and kidneys and also developed hematological abnormalities. Liver was also involved as reflected by deranged liver function tests (LFTs). He was also positive for anti-HCV and HCV PCR was positive. The deranged LFTs might reflect HCV hepatitis, but his liver functions improved without anti-HCV therapy, implying that liver involvement was most probably secondary to microvascular thrombosis. We performed renal biopsy and this showed evidence of thrombotic microangiopathy (TMA). Our patient gave history of fever, which subsided soon with therapy. Infection most probably was the precipitating factor in this case; however, the nature of infection could not be established in this case, as the blood and urine cultures were negative.

Clinically, manifestations of CAPS reflect consequences of acute widespread microvascular thrombosis with multi-organ failure. Hence, its clinical differential diagnosis is broad and includes hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC) and heparin-induced

thrombocytopenia (HIT), among others. All these differentials were considered in our case and were ruled out by careful clinical, laboratory and coagulation work-up (Table 3). In fact, almost all of these conditions are characterized by microvascular injury and thrombosis; hence, there is marked overlap among the features of these diseases. It is essential to rule out some of the above conditions, because there are differences in the management of some of these conditions. However, sometimes it can be a real challenge to make a correct diagnosis. Although, there was severe thrombocytopenia and anemia, there were no schistocytes on peripheral blood film and D-dimers were within normal range in our case. Coagulation profile was also not significantly deranged and there was no bleeding tendency. No history of abdominal pain or central nervous system was present. Blood pressure was also within normal range. Most importantly, the aPLA antibodies were positive. All these features helped us to rule out the above differential diagnostic entities and reached at the correct diagnosis.

Detailed descriptions of histopathological alterations in CAPS are scanty [3, 7]. The few studies that have included histopathological findings have shown that the main lesions consist of microvascular thrombosis and its consequences. In our case, renal biopsy was performed slightly later in the course of the disease and it showed the consequences of ischemic injury to renal parenchyma, including the glomeruli, arterioles and tubules. No active thrombotic lesions were found. An occasional glomerulus did show residual endocapillary hypercellularity, reflecting endothelial cell swelling and proliferation and double contouring of capillary walls, suggestive of chronic endothelial injury of some duration. One glomerulus also showed evidence of subtle and segmental mesangiolysis, resulting in aneurysmal dilatation of some capillary loops. Microvasculature showed evidence of repair in the form of double contouring of glomerular capillary walls and intimal proliferation in arterioles. These features constitute the morphological hallmarks of chronic or organizing

Table 3 A list of conditions which enter into the differential diagnosis of catastrophic antiphospholipid antibody syndrome (CAPS) and their distinctive features

	CAPS	HUS	TTP	DIC	Malignant hypertension
Fever	++	+	++	±	–
Hypertension	+	±	±	±	+++
Abdominal pain	++	++	–	–	–
Renal disease	++	+++	+	+	++
CNS disease	+	±	+++	–	+++
MAHA	++	+	+++	±	±
Thrombocytopenia	+++	++	+++	±	±
Schistocytes	±	++	++	±	±
Coagulopathy	++	±	±	+++	±
aPLA	Present	–	–	–	–
ADAMTS-13	Normal	Low/absent	<5%/absent	Normal	Normal

aPLA antiphospholipid antibody, ADAMTS-13 A Disintegrin and Metalloproteinase with Thrombospondin motifs, CAPS catastrophic antiphospholipid antibody syndrome, DIC disseminated intravascular coagulation, HUS hemolytic uremic syndrome, MAHA microangiopathic hemolytic anemia, TTP thrombotic thrombocytopenic purpura

phase of TMA. The renal biopsy findings vary depending on the duration of the disease process [12, 13]. In the acute phase of disease, fibrin thrombi are typically seen in the microcirculation in nearly all cases of CAPS, as opposed to primary APS (PAPS) or systemic lupus erythematosus-APS (SLE-APS); the later two conditions show acute TMA lesions in around one-third of cases [12, 13]. In our case, renal biopsy was delayed because of thrombocytopenia and impaired coagulation parameters; hence, the biopsy changes were predominantly reflective of consequences of TMA and subsequent repair phenomenon. It is important to recognize the chronic form of TMA, as it is easily missed and can have serious implications. Mild chronic cases may also have implications for live-related transplants.

We treated the patient aggressively with combination therapy including plasmapheresis, anticoagulation and supportive renal replacement therapy. We did not use corticosteroids, which form an important part of combination therapy, because our patient was HCV RNA positive [14]. Luckily, we were able to save the patient as well as his kidney, at least for some time. There was some chronic damage in the kidney, which could persist. But with proper treatment and follow-up, progression of renal deterioration can be stopped.

In conclusion, this case highlights the need to keep CAPS in the differential diagnosis of any patient with rapidly developing multi-organ failure along with ischemic or bleeding manifestations. Early treatment can save life in such cases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this case report were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References

1. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. *Autoimmun Rev*. 2010;10:74–9.
2. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295–306.
3. Erkan D, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum*. 2003;48(12):3320–7.
4. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12(7):530–4.
5. Bucciarelli S, Erkan D, Espinosa G, et al. Catastrophic antiphospholipid syndrome: treatment, prognosis, and the risk of relapse. *Clin Rev Allergy Immunol*. 2009;36(2–3):80–4.
6. Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol*. 1992;19:508–12.

7. Piette JC, Cervera R, Levy RA, Nasonov EL, Triplett DA, Shoenfeld Y. The catastrophic antiphospholipid syndrome—Asherson's syndrome. *Ann Med Intern (Paris)*. 2003;154:195–6.
8. Erkan D, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum*. 2003;48:3320–7.
9. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome (CAPS): international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12:530–4.
10. Vora SK, Asherson RA, Erkan D. Catastrophic antiphospholipid syndrome. *J Intensive Care Med*. 2006;21:144–59.
11. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)*. 2001;80:355–77.
12. Tektonidou MG, Sotsiou F, Moutsopoulos HM. Antiphospholipid syndrome (APS) nephropathy in catastrophic, primary, and systemic lupus erythematosus-related APS. *J Rheumatol*. 2008;35(10):1983–8.
13. Gupta RK, Liu E, Bonilla E, Elsaid H. Histopathology of catastrophic antiphospholipid syndrome-associated nephropathy in a SLE patient without concurrent lupus nephritis. *Arthritis Rheumatol*. 2020;72(1):149.
14. Cervera R, Bucciarelli S, Plasín MA, Gómez-Puerta JA, Plaza J, Pons-Estel G, Catastrophic Antiphospholipid Syndrome (CAPS) Registry Project Group (European Forum On Antiphospholipid Antibodies), et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". *J Autoimmun*. 2009;32(3–4):240–5.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.