Catastrophic antiphospholipid syndrome: literature review and case report

Houda Ben Soltane [1.2], Rebeh Baazaoui [2], Ons Haddaji [2], Fatma Lihiou[1.2], Mariem Khrouf[1.2], Anis Haj Hassine[1.2], Fatma Kacem[2], Zied Mezgar [1.2.]

1: Emergency Department, Farhat Hached University Hospital, Sousse, Tunisia
2: Faculty of Medicine of Sousse; 4002. University of Sousse, Tunisia.
Corresponding author: *Ons Haddaji; Email: ons.haddaji.s@gmail.com; Phone number: 58646146*

Abstract

Catastrophic antiphospholipid syndrome (CAPS) is a rare and life-threatening condition characterized by the simultaneous occurrence of multiple thrombotic events, predominantly affecting microcirculation. We report a case of CAPS in a 55-year-old male patient with no notable pathological history who presented with diffuse abdominal pain and subsequently developed neurological and renal manifestations. This case report is complemented by a comprehensive literature review of CAPS, highlighting its epidemiology, clinical manifestations, diagnostic criteria, and treatment options.

Our literature review included a thorough search of various databases and search engines, including PubMed/Medline, Google Scholar, and Cochrane, in both English and French. We adhered to patient data protection guidelines, ensuring confidentiality throughout the report.

CAPS is associated with a significant morbidity and mortality rate, with a high short-term mortality rate, particularly in the acute phase. Prompt recognition and early initiation of treatment, such as the "Triple Therapy" approach involving intravenous heparin, oral anticoagulation, and corticosteroids, are crucial for improving patient outcomes. In refractory cases, Rituximab and Eculizumab have shown promise as alternative treatment options.

Our case report underscores the importance of timely diagnosis and appropriate management of CAPS. Further research and collaboration among healthcare professionals are warranted to enhance our understanding of this complex syndrome and improve patient care.

Keywords: Catastrophic antiphospholipid syndrome, thrombosis, microcirculation, autoimmune.

INTRODUCTION

Antiphospholipid syndrome (APS) or Hughes syndrome is a clinical and biological entity characterized by the association of thromboembolic (venous and/or arterial) and/or obstetric manifestations and long-lasting antiphospholipid antibodies (lupus-like circulating anticoagulant; IgG or IgM anti-B2 glycoprotein I or IgG or IgM anti-cardiolipin antibodies) (1,2). Less than 1% of patients with APS develop a rare and severe variant known as

the catastrophic variant, or CAPS or Asherson syndrome. This entity is characterized by the occurrence of multiple microcirculatory thromboses within a short period, often leading to a multivisceral failure. CAPS commonly occurs in young women during primary APS (60%) (3). The prognosis is poor, with a high mortality rate estimated at 30% in the acute phase and 34% at one year (3).

This case report presents a unique instance of primary CAPS diagnosed early in a 55-year-old male patient without any apparent triggering factors. The patient showed a favorable outcome with dual therapy. Additionally, the literature on this condition is reviewed to provide a comprehensive understanding of CAPS.

METHODS

We report an observation of catastrophic antiphospholipid syndrome, with a literature review of the existing literature on this topic.

To gather relevant information, a thorough search was conducted using various databases and search engines, including PubMed/Medline, Google Scholar, and the Cochrane database. The search encompassed both English and French sources, with a focus on accessing full-text articles or published abstracts.

Throughout the process, strict adherence to patient data protection regulations was maintained. The confidentiality and anonymity of the patient were carefully preserved, ensuring that no identifying information was disclosed at any point from data collection to publication.

RESULTS

We present a case study of a middle-aged Tunisian man, Mr. A.B, who had no significant medical history and was admitted to the emergency department due to persistent diffuse abdominal pain for the past 7 days without any gastrointestinal or urinary tract-associated symptoms.

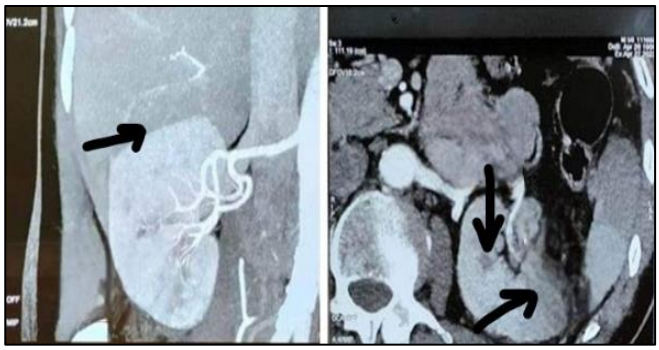
On physical examination, the patient's hemodynamic, respiratory, and neurological status were stable with tachycardia at 110 bpm; no fever was documented upon initial examination.

He presented with diffuse abdominal tenderness without guarding or contracture, free hernial orifices; the rectal exam was without abnormalities.

Upon further investigations:

- EKG: RRS 85 bpm; axis 60°; no repolarization disorders; LVH (Sokolow index 40)
- Biology:
  - Hb= 16 g/dl; WBC= 15000/mm3 with 75% PNN; platelets= 198000
- Creatinine: 97 µmol/l (clearance=74 ml/Mn).
- Na+=137 mmol/l; K+= 4.7 mmol/l; Cl- = 98.73 mmol/l. CRP = 41 mg/l; blood calcium = 2.64 mmol/l; Procalcitonin = 0.05 ng/ml
- ALT = 164UI/L (5×ormal values); ASAT = 62UI/L; BT/BD=6/1; GGT= 58 UI/L; PAL 99 UI/L. CBEU: Hu +++; Alb: +; Leu: 17/mm3.
- Blood cultures were negative.

A contrast injection abdominal pelvic CT scan revealed multiple foci of infarction in both kidneys and the spleen, direct images of clot in a superior polar branch of the left renal artery, and in the middle part of the superior mesenteric artery.



Figures 1+2: CT scans showing foci of infarction in both kidneys and the left renal artery.

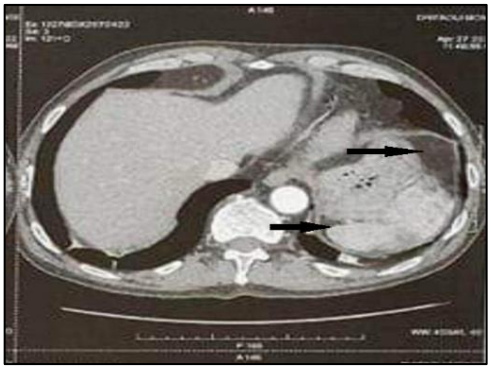


Figure 3: CT section showing foci of infarction in the spleen.

Given the arterial location of the emboli, a TEE and a TTE were performed to look for a cardiac origin, and concluded that the left atrium was filled to 3 thrombi, one of which was floating, measuring 8×8 mm; the cavities were not dilated; there was no valvular disease; and there was no image suspicious of infectious endocarditis. The patient was put on effective anticoagulation: UFH at PSE combined with methylprednisolone (1mg/kg/d). After 3 days, the patient became confused with the onset of right hemiplegia and dysarthria. A cerebral CT scan concluded that there was an area of non-systematic hypodensity in the left frontal subcortical white matter. A cerebral MRI-MRA had concluded with a recent ischemic stroke in the left superficial middle cerebral territory.

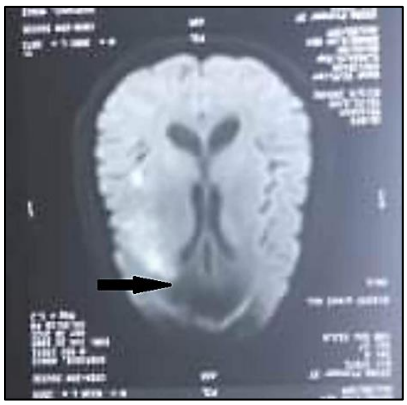


Figure 4: MRI slide showing left superficial middle cerebral ischemic stroke

While the goal of anticoagulation was achieved, the patient's neurological condition worsened around the 7th day of treatment, with a GCS of 12/15, with the onset of left hemiparesis. A cerebral CT scan confirmed the presence of an ongoing ischemic stroke in the territory of the right superficial middle cerebral artery. The contralateral first stroke showed a stable appearance without hemorrhagic transformation. Given the multiplicity of thromboses and their unusual anatomical location, especially in the abdomen, further investigation was conducted to identify a systemic origin.

The etiological work-up included a thorough physical examination, which did not reveal any vascular abnormalities upon auscultation of various vascular axes. Ophthalmological examination yielded normal results. Tests for rheumatoid factor RF, anti-cyclic citrullinated peptide (anti-CCP) antibodies, and

cryoglobulinemia were negative. The levels of complement components C3 and C4 were within the normal range. Proteinuria was absent in the 24-hour urine sample. Serological tests for viral hepatitis B and C, syphilis, and HIV were negative. Protein C, protein S, and antithrombin III levels were normal. Furthermore, there was no indication of resistance to activated protein C or the presence of the factor V Leiden mutation.

The activated partial thromboplastin time was not prolonged, and levels of fibrinogen and homocysteine were within the normal range.

The immunological work-up found:

- aCL antibody: IgM positive at 93 MPL/ml, IgG negative; IgA negative.
- aB2GPI antibody: IgM positive at 133 IU/ml, IgG negative; IgA negative.
- LA: positive.
- Anti-nuclear antibodies; anti-native DNA; anti-neutrophil cytoplasm negative.

Biological control at 12 12-week intervals still found positive aCL, thus the diagnosis of primary APLS was retained.

Given the rapidity and multiplicity of thrombotic events, the diagnosis of CAPS was retained. The patient is currently on warfarin (INR=3) and Atorvastatin 40mg with a good clinical evolution: GCS: 15/15; regression of neurological deficit and dysarthria. No new thrombotic events were noted.

DISCUSSION

APS is now recognized as the most common cause of acquired thrombophilia (4). APS is a thrombogenic autoimmune disorder whose pathophysiological mechanisms are not yet well understood. In vitro studies have shown that antiphospholipid antibodies (aPL) have pro-thrombotic properties and effects on platelet activation (2).

APS is defined by the combination of at least one clinical and at least one biological criterion among those listed in Table 1, persisting at least 12 weeks. (5,6)

Table 1: APLS diagnostic criteria

Clinical criteria	Biological criteria
Arterial or venous thrombotic events obstetric events: * Unexplained fetal loss after 10 weeks' gestation, * Premature delivery before 34 weeks' gestation * at least 3 unexplained early spontaneous miscarriages (before 10 weeks' gestation).	Presence of lupus anticoagulant (LA) IgG and/or IgM anticardiolipin antibodies (aCL), or IgG anti-beta 2 glycoprotein I (b2GP1) antibodies and/or IgM, confirmed at 12-week intervals. aCL and ab2GP1 by ELISA above the 99th percentile.

A literature review found publications of case reports or small case series, given the rarity of this condition. We chose to focus on the international registry, or "CAPS registry". The following table summarizes the epidemiological and clinical characteristics of these observations in the chronological order of their appearance.

The immunological work-up of our patient is marked by a triple positivity: IgM-positive anti-cardiolipin antibodies at 93 MPL units; IgM-positive anti-beta 2-glycoprotein I antibodies at 133 MPL units, and the presence of anticoagulant lupus.

Table 1. Review of the literature on the CAPS registry

Author/references	Year	Number of cases	Epidemiological and evolutionary criteria
Asherson RA (7)	1992	10	90% Females, mean age = 39years, 60% primary APLS, 30% SLE, organ involvement: 50% cerebral, 50% cardiac, 50% pulmonary, 60% abdominal, 50% skin, mortality =40%
Asherson RA (5)	2003	50	66% Females, mean age = 37years, 56% Primary APLS, 30% SLE, precipitating factor 22%, mortality50%
Cervera R (8)	2005	220	69% females, mean age = 38years, organ involvement: renal 70%, pulmonary 66% cerebral 60% cardiac 52% skin 47%, mortality 48%
Rodriguez-pinto I (9)	2016	500	69% females, mean age = 38years, 75% SLE, precipitating factor 65%, mortality 37%
Lopez-Benjume B (10)	2022	584	39 cases (6.7%) treated with eculizumab, first intention treatment in 6 cases, palliative 30cases, mortality rate = 5/39

Antiphospholipid syndrome (APS) encompasses both primary APS and secondary APS associated with other systemic diseases. Primary APS affects approximately 0.5% of the population, with a higher prevalence in women: 3.5 women/1man, with an average age of 34 years. It is characterized by arterial thrombosis and recurrent miscarriages. (11)

Secondary APS can occur in the context of various systemic diseases, such as scleroderma, Behçet's disease, Sjögren's syndrome, Dermatomyositis, neoplasia, hematological disorders, coagulation protein deficiencies, infectious diseases, or because of certain medications such as Phenothiazines (chlorpromazine, hydantoins), beta-blockers, interferon alpha, quinidine.

In our patient, no clinical or biological criteria for SLE were found. C3 and C4 supplements were normal. NAA, native anti-DNA, and neutrophil cytoplasm tests were negative. Serologies for hepatitis B and C were negative. Similarly, the tests for RF and Cryoglobulinemia were negative. The APTT was not prolonged. Biological control at a 12-week interval still found aCL, ab2GPI, and LA positive, thus the diagnosis of primary APS was retained.

Catastrophic antiphospholipid syndrome (CAPS), also known as Asherson syndrome, is a rare but severe manifestation of APS. While it affects less than 1% of APS patients, the number of reported cases has significantly increased over the years. In Tunisia, six cases of CAPS have been documented. CAPS is characterized by the simultaneous occurrence of multiple microcirculatory thromboses, often leading to multivisceral failure. Arterial or venous macro thrombosis can sometimes be associated (3,12).

In fact, it is the rapidity and multiplicity of thrombotic events that differentiate CAPS from classic SAPL (12). It can be distinguished from classic APS by the rapidity and multiplicity of thrombotic events. However, the rarity of CAPS poses challenges in systematic study and conducting randomized clinical trials. The CAPS Registry, comprising 1205 registered patients, provides valuable clinical, laboratory, and therapeutic data. CAPS predominantly affects young individuals, with a mean age of 38 years,

and women account for 69% of cases (13). It occurs equally in primary APS and APS associated with other autoimmune diseases, particularly systemic lupus (5). CAPS can also serve as an initial presentation of APS in approximately 50% of cases (14). Our case involved a primary CAPS in a 55-year-old man.

The clinical manifestations of catastrophic antiphospholipid syndrome are influenced by four factors: microcirculatory involvement, systemic inflammatory response syndrome (SIRS) manifestations, activation of coagulation inhibitors and lysis, and complement activation.

Thrombus development and the risk of recurrent thrombotic events are associated with high levels of lupus anticoagulant (LA) and anticardiolipin antibodies (aCL). CAPS can affect multiple organs, with renal involvement being the most common (73% of cases), often presenting as lumbar pain, fever, acute renal failure, proteinuria, hypertension, and microscopic hematuria (15). Our patient presented with bilateral low back pain and microscopic hematuria. The CT scan showed multiple foci of infarction in both kidneys, with a direct image of a clot in the left renal artery.

Neurological damage is also frequent, leading to encephalic suffering (40% of the cases), vigilance disorders, confusion, headaches, or seizures. Similarly, constituted cerebral microinfarcts were observed in 40% of cases (13). Our patient presented a confusional syndrome and two ischemic strokes in the territory of the superficial middle cerebral artery on each side.

Cardiac manifestations may include heart failure (44% of the cases), myocardial infarction (30%), valvulopathy (10%), intracardiac thrombi, and/or Libman-Sacks endocarditis (16). In our patient, 3 thrombi were found in the left atrium, one of which was floating.

Pulmonary manifestations such as acute respiratory distress syndrome (26%), intra-alveolar hemorrhage (12%), and pulmonary Edema (8%) can occur (13). Abdominal and digestive manifestations are less common (10%), with liver failure (9%) and jaundice (7%) observed in some cases (13,17–22). Our patient had hepatic cytolysis (5×normal values), CT scan showed splenic infarction and a clot pattern in the superior mesenteric artery.

Vascular thromboembolic events, including deep vein thrombosis (69%) and pulmonary embolism (26%), are common systemic manifestations (13). In our patient, the involvement was purely arterial.

Skin involvement (50% of the cases) can manifest as reticular livedo, acrocyanosis, skin necrosis, ischemic gangrene, and sub-nail hemorrhage (23). In our patient, no skin involvement was noted.

Infections, discontinuation or modification of antithrombotic therapy, surgery, and pregnancy can precipitate CAPS.

The biological disturbances include both long-lasting abnormalities associated with APS and non-specific abnormalities concurrent with the acute microangiopathy, such as thrombocytopenia <100,000/mm3 (46%), mechanical hemolytic anemia (35%), and signs of disseminated

intravascular coagulation (15%) (19,20). In the reported patient, there were no findings of anemia or thrombocytopenia.

Triggers have been identified in approximately 65% of cases, with the most common trigger being infection. Other triggers include surgical procedures or trauma, withdrawal of anticoagulation medication, SLE flares, and oral contraceptive drugs (13). CAPS should be differentiated from a thrombotic storm occurring outside of APS.

In the absence of histological evidence of vascular occlusion, our patient met the criteria for probable de novo CAPS. It was indicative of APS, and no triggering factors were found. Preliminary Classification Criteria for Catastrophic Antiphospholipid Syndrome are: (23,24)

- Evidence of involvement of three or more organs, systems, and/or tissues
- Development of manifestations simultaneously or in less than a week
- Confirmation by histopathology of small-vessel occlusion
- Laboratory confirmation of the presence of antiphospholipid antibodies

Regarding CAPS treatment, the grades of evidence are quite low in the absence of clinical trials, due to the extreme rarity of the syndrome. The gold standard treatment for catastrophic antiphospholipid syndrome (CAPS) is the "Triple Therapy" approach. It consists of three main components:

1. Anticoagulation: Intravenous heparin is administered during the acute phase, followed by long-term oral anticoagulation to prevent further blood clot formation.

2. Corticosteroids: High-dose intravenous methylprednisolone followed by oral prednisone is used to reduce inflammation and modulate the immune response.

3. Intravenous Immunoglobulin (IVIg) or Plasma Exchange: IVIg is the first-line treatment for critically ill patients, while plasma exchange may be used to remove antiphospholipid antibodies and procoagulant factors.

In refractory cases, additional therapies such as rituximab and eculizumab may be considered. However, evidence is still scarce, and there are only anecdotal case reports.

Treatment should also address any underlying factors contributing to CAPS. Overall, a multidisciplinary approach and individualized management are crucial for the successful treatment of CAPS. (9,25–31)

CAPS is associated with high morbidity and mortality. Overall mortality during the acute phase is close to 37% [8]. Short-term mortality is associated with the presence of neurological, cardiac, or pulmonary involvement, associated systemic lupus, and, above all, the absence of anticoagulant treatment. The prognosis of CAPS remains severe in the long term, with a 1-year mortality of around 34% (23).

Prevention of CAPS is essential and relies on adequate management of the perioperative period

when surgery cannot be avoided, prompt treatment and prevention by vaccination of infections, and education of patients with APS, particularly in the management of oral anticoagulants (27). Studies agree on the effectiveness of very prolonged anticoagulation.

Associated risk factors for thrombosis and atherosclerosis must be controlled. In our patient, he received dual therapy in the acute phase: UFH at PSE combined with methylprednisolone (1mg/kg/d) followed by a relay with warfarin. The aim was to achieve an INR close to 3 with a good clinical outcome. No new thrombotic events were noted.

CONCLUSION

In conclusion, catastrophic antiphospholipid syndrome (CAPS) is a rare and severe manifestation of antiphospholipid syndrome (APS) characterized by the rapid onset of multiple thrombotic events, often involving the microcirculation. CAPS can affect various organs and systems, leading to significant morbidity and mortality. It is essential to recognize the clinical features of CAPS promptly and differentiate it from classic APS or other thrombotic conditions.

Further research and clinical studies are needed to improve our understanding of CAPS, enhance early diagnosis, and identify more effective treatment strategies. Collaborative efforts among healthcare professionals, researchers, and patients are essential for advancing knowledge and improving the management and outcomes of CAPS patients.

Conflict of interest and funding sources: The authors declare no conflicts of interest and no funding sources for this study.

Generative AI use: An AI program (DeepL write) was used for linguistic correction and improving the coherence of the manuscript.

REFERENCES

1. Kalman DR, Khan A, Romain PL, Nompleggi DJ. Giant gastric ulceration associated with antiphospholipid antibody syndrome. Am J Gastroenterol1996. 91:1244–7.

2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, BreyRL CR. International consensus statement on an update of the classification criteriafor definiteantiphospholipid syndrome (APS. J Thromb Haemost. 2006; 4:295–306.

3. Carmi O, Berla M, Shoenfeld Y, Levy Y. Diagnosis and management of catastrophic antiphospholipid syndrome. Expert Rev Hematol. 2017 Apr 3;10(4):365–74.

4. Hachula E, Piette AM, Hatron PY, Bletry O. Aspirin and anti-phospholipid syndrome. Rev Med Int. 2000;21 Suppl 1:83–8.

5. Asherson RA, Cervera R, De Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003 Jul;12(7):530–4.

6. Aguiar CL, Erkan D. Catastrophic antiphospholipid syndrome: how to diagnose a rare but highly fatal disease. Ther Adv Musculoskelet Dis. 2013;5(6):305–14.

7. Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol. 1992 Apr;19(4):508–12.

8. Cervera R. CAPS Registry. Lupus. 2012 Jun 1;21(7):755–7.

9. Rodriguez-Pinto I. Catastrophicantiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the international CAPS Registry.AutoimmunityReviews. Vol. 15. Pages: 2016. p. 1120–4.

10. López-Benjume B, Rodríguez-Pintó I, Amigo MC, Erkan D, Shoenfeld Y, Cervera R, et al. Eculizumab use in catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis from the "CAPS Registry." Autoimmun Rev. 2022 Apr;21(4):103055.

11. Petri M. Epidemiology of the antiphospholipid antibody syndrome. J Autoimmun. 2000 Sep;15(2):145–51.

12. Bucciarelli S, Cervera R, Espinosa G, Gomez-Puerta JA, Ramos-CosalsM F, J. Mortality in the catastrophic typhospholipid syndrome: causes of death and prognostic factors. AutoimmunRev. 2006 Aug;6:72–5.

13. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016 Dec;15(12):1120–4.
14. Cervera R, CAPS Registry Project Group. Catastrophic antiphospholipid syndrome (CAPS): update from the "CAPS Registry." Lupus. 2010 Apr;19(4):412–8.
15. Fakhouri RE DMJ, M A. Antiphospholipid syndrome presenting as episodic limb ischemia. Arch Child. 1996; 75:342–53.
16. Pons I, Jeréz A, Espinosa G, Rodríguez-Pintó I, Erkan D, Shoenfeld Y, et al. Cardiac involvement in the catastrophic antiphospholipid syndrome (CAPS): Lessons from the "CAPS registry." Semin Arthritis Rheum. 2024 Jun 1; 66:152439.
17. Lambert M, Darnige L, HEL, S.A.P.L. Centre de référence des maladies autoimmunes et des maladies systémiques rares. Department of Internal Medicine. Hôpital Claude Huriez. CHRU;
18. R. C, I. RP, G E. Diagnosis and clinical management of catastrophic antiphospholipid syndrome: a comprehensive review. J Autoimmun. 2018;92:1–11.
19. CuadradoMJ, M.J., E M. Thrombocytopenia in the antiphospholipidsyndrome. Ann Rheum Dis. 1997;56:194–6.
20. ViannaJL KMA, J OR. Comparison of the primary and secondaryantiphospholipidsyndrome: A European multicenter study of 114 patients. Ann Med. 1994;23(1):41–5.
21. N. CC, I. C, V. LG, N. M, G. L, R. P. Review on catastrophic antiphospholipid syndrome. Press Med. 2016;45(12 Pt 1):1084–92.
22. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid syndrome. A systematic review. JAMA. 2006;295(9):1050–7.
23. Chambrun M. P, A. M, C-Edouard L, A C, Z A. New developments in antiphospholipid antibody syndrome in intensive care. Médecine Intensive Réanimation. 2021;30(4):341–54.
24. Francès C, BareteS S, A. Dermatologicmanifestations of the antiphospholipid syndrome. J Intern Med. 2012;33:200–5.
25. Cervera R, Rodríguez-Pinto I, Espinosa G. Catastrophic antiphospholipid syndrome: Task force report summary. Lupus. 2014;23:1283–5.
26. Kazzaz NM, McCune WJ, Knight JS. Treatment of catastrophic antiphospholipid syndrome. Curr Opin Rheumatol. 2016;28:218–27.
27. Tenti S, Cheleschi S, Guidelli GM. Intravenous immunoglobulins and antiphospholipid syndrome: How, when, and why? A review of the literature. Autoimmun Rev. 2016;15:226–35.
28. Berman H, Rodríguez-Pintó I, Cervera R. Rituximab use in the catastrophic antiphospholipid syndrome: Descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev. 2013;12:1085–90.
29. Strakhan M, Hurtado-Sbordoni M, Galeas N. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: A case report and review of literature. Case Rep Hematol. 2014;2014(704371).
30. Shapira I, Andrade D, Allen SL. Induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Arthritis Rheum. 2012;64:2719–23.
31. Lonze BB, Zachary AA, Magro CM. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. Am. J Transpl. 2014;14:459–65.