Case of catastrophic antiphospholipid syndrome presenting as neuroretinitis and vaso-occlusive retinopathy

Young In Yun †, Ji Hyun Kim †, Seon Hee Lim, Yo Han Ahn, Hee Gyung Kang, Il-Soo Ha and Baek-Lok Oh *

Abstract

Background: Ocular involvement in catastrophic antiphospholipid syndrome (CAPS), a rare, life-threatening form of antiphospholipid syndrome (APS) that results in multiorgan failure and a high mortality rate, has rarely been reported.

Case presentation: A 15-year-old girl presented with sudden vision blurring in both eyes. She had marked optic disc swelling and macular exudates in the right eye and intra-arterial white plaques, a few retinal blot hemorrhages, and a white ischemic retina in the left eye. Systemic examination revealed she had acute kidney injury with thrombotic microangiopathy (TMA), multiple cerebral infarcts, valvular dysfunction, and a high titer of triple aPL. Thus, she was diagnosed with CAPS involving the brain, eyes, heart, and kidneys. Plasma exchange and the administration of glucocorticoids, immunoglobulin, warfarin, and rituximab brought a sustained recovery of the TMA, visual symptoms, and echocardiographic findings.

Conclusions: Ocular involvement of both vaso-occlusive retinopathy, an APS-related thrombotic microangiopathy, and neuroretinitis, a non-thrombotic microangiopathy, can occur as an initial presentation of CAPS.

Keywords: Catastrophic antiphospholipid syndrome, Antiphospholipid syndrome, Neuroretinitis, Vaso-occlusive retinopathy, Thrombotic microangiopathy

Background

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and venous thrombosis that is induced by antiphospholipid antibodies (aPL): lupus anticoagulant (LA), anticardiolipin, and anti-beta2-glycoprotein I (anti-β2-GPI). Catastrophic APS (CAPS) is a rare, life-threatening form of APS that results in multiorgan failure and a high mortality rate.

The most frequently involved sites in CAPS are the kidneys (73%), lungs (60%), brain (56%), and heart (50%) [1, 2]. Ocular involvement in CAPS has rarely been reported [3–5]. We report the first case of CAPS in an adolescent girl with concurrent vaso-occlusive retinopathy and neuroretinitis, which may reflect microangiopathies from thrombotic and non-thrombotic pathophysiology of APS, respectively.

Case presentation

A 15-year-old girl presented to Seoul National University Hospital on December 17, 2018 with sudden vision blurring in both eyes that started 8 days prior. She previously had episodes of transient right arm...
weakness and dysarthria 22 and 6 months before, respectively, but no medical attention was sought. She was not on any medication, and ophthalmic history was negative. At presentation, she had dysuria, frequency, urgency and gross hematuria with mild fever. Her blood pressure was 171/135 mmHg. She was otherwise healthy and no family or trauma history was noted.

Her corrected visual acuities were 20/50 in the right eye and 20/35 in the left eye. Ophthalmic examination revealed marked optic disc swelling and macular exudates in the right eye (Fig. 1a). In the left eye, in addition to mild disc swelling and macular exudates, intra-arterial white plaques, a few retinal blot hemorrhages, and a white ischemic retina were observed (Fig. 1b). Fluorescein angiographies revealed disc and vascular leakage with decreased choroidal perfusion in both eyes, and retinal arterial occlusions with large non-perfusion area at temporal retina was observed in the left eye (Fig. 1c and d). Optical coherence tomography (OCT) images confirmed bilateral disc edema and the left eye (Fig. 1c and d). OCT scans revealed superior and temporal retinal thinning in the left eye (Fig. 2f). Visual field test showed a nasal field defect in the left eye, which was consistent with the non-perfused area in the temporal retina (Fig. 2g).

**Discussion and conclusions**

CAPS is associated with a high mortality rate; therefore, early detection and aggressive therapy are very important [6, 7]. Currently, the expert consensus recommends the use of the so-called ‘triple therapy’ for CAPS: glucocorticoids, plasma exchange or IVIG, and anticoagulation therapy regardless of the severity of thrombocytopenia [1, 8–10]. The exact pathogenesis of APS/CAPS has not been fully elucidated. However, both a thrombotic mechanism, which is caused by the aPL-induced hypercoagulable state and a triggering factor (two-hit theory) [7], and a non-thrombotic mechanism, which is presumably caused by aPL-induced endothelial cell dysfunction [11–16], have been suggested. Complement activation also has a pathogenic role in thrombotic APS, aPL-induced thrombosis, and endothelial cell injury [17, 18]. In our patient, complement levels were marginally decreased, which indicated complement activation as reported by Oku et al. [19] and Barratt-Due et al. [20].

As per the findings from the CAPS Registry by Cer- vera et al. [1], the most common triggering factor for CAPS is infection (46.7%), which is more prevalent in children than adults according to Berman et al. [21]. In our patient, CAPS may have been triggered by acute pyelonephritis under her untreated APS.

Ocular involvement as an initial presentation of CAPS has been rarely reported [3, 22]. Vasooclusive retinopathy is a microangiopathy with diffuse capillary non-perfusion and small arterial or arteriolar occlusions in the retina, which has a very poor visual prognosis due to the high rate of neovascularization and/or vitreous hemorrhage [23]. Pathological findings in vaso-occlusive retinopathy are microthrombosis and immune complex-mediated vasculopathy [24]. Thus, the vaso-occlusive retinopathy in our patient could be considered a usual finding of TMA in APS.

Plasma exchange and the administration of glucocorticoids, intravenous immunoglobulin (IVIG), warfarin, and rituximab brought a sustained recovery of the TMA, visual symptoms, and echocardiographic findings. Retinal scatter laser treatments were performed in her left eye to prevent neovascularization of the avascular retina. Six months after presentation, her corrected visual acuities were 20/20 in both eyes, and the fundus showed no disc edema with few remnant exudates (Fig. 2a, b). OCT scans revealed superior and temporal retinal thinning in the left eye (Fig. 2f). Visual field test showed a nasal field defect in the left eye, which was consistent with the non-perfused area in the temporal retina (Fig. 2g).
Neuroretinitis is a descriptive term for optic neuropathy that is characterized by optic disc swelling with macular exudates. It is related to abnormal permeability of capillaries deep within the optic disc caused by an infectious process or inflammation. Only one other case of neuroretinitis with a non-infectious origin as an initial manifestation of APS/CAPS has been reported [3]. In the previous case and in ours, there was no evidence of occlusion of the optic disc vasculature and visual function was restored with appropriate treatment. Therefore, in contrast to the vaso-occlusive retinopathy caused by
thrombotic pathophysiology, neuroretinitis in this case was presumably caused by a non-thrombotic aPL-induced endothelial cell dysfunction, which has been suggested to be involved in the development of non-thrombotic renal, cerebral, and cardiac lesions in APS patients [25].

In summary, this is a report of a patient with CAPS who initially presented with a rare ocular involvement showing APS-related thrombotic and
non-thrombotic microangiopathies. Early diagnosis and timely intervention were crucial for the maintenance of visual function and the survival of this patient.

Abbreviations
CAPS: Catastrophic antiphospholipid syndrome; APS: Antiphospholipid syndrome; aPL: Antiphospholipid antibodies; TMA: Thrombotic microangiopathy; LA: Lupus anticoagulant; anti-ß2-GPI: Anti-beta2-glycoprotein I

Acknowledgements
None.

Authors’ contributions
YY and JK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. SL, YA, and HK designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. IH and BO conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding
None.

Availability of data and materials
All data supporting the conclusions of this article are included in this published article.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient’s parent or guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Ophthalmology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea. 2Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, South Korea. 3Department of Pediatrics, Seoul National University Children’s Hospital, Seoul, South Korea.

Received: 18 September 2020 Accepted: 3 December 2020
Published online: 09 December 2020

References
1. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, et al. 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. Autoimmun Rev. 2014;13(7):699–707.
2. Rodríguez-Pintó I, Molinino M, Santacreu I, Shoenfeld Y, Erkan D, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the international CAPS registry. Autoimmun Rev. 2016;15(12):1120–4.
3. Farooqui SZ, Thong BY, Teoh SC. Neuroretinitis as an initial presentation of lupus-like illness with antiphospholipid syndrome. Lupus. 2010;19(14):1662–4.
4. Kurz DE, Wang RC, Kurz PA. Idiopathic retinal vasculitis, aneurysms, and neuroretinitis in a patient with antiphospholipid syndrome. Arch Ophthalmol. 2012;130(2):257–8.
5. Moosavi M, Hosseini SM, Shoebi N, Ansari-Astaneh M-R. Unilateral idiopathic retinal vasculitis, aneurysms, and neuroretinitis syndrome (IRVAN) in a young female. J Curr Ophthalmol. 2015;27(1–2):63–6.
6. Cervera R, Font J, Gómez-Puerta JA, Estepa G, Cuchillo I, et al. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis. 2005;64(8):1205–9.
7. Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, et al. Infectious origin of the antiphospholipid syndrome. Ann Rheum Dis. 2006;65(1):122–6.
8. Joshi U, Afroz S, Ranka S, Mba B. Bilateral central retinal artery occlusion from catastrophic antiphospholipid syndrome. BMJ Case Rep. 2018. https://doi.org/10.1136/bcr-2018-226463.
9. Kazzaz NM, McCune WJ, Knight JS. Treatment of catastrophic antiphospholipid syndrome. Curr Opin Rheumatol. 2016;28(3):218.
10. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. New Engl J Med. 1995;332(15):993–7.
11. Mayer M, Cervera M, Radiol M, Ćiček N. Antiphospholipid syndrome and central nervous system. Clin Neurol Neurosurg. 2010;112(7):502–8.
12. Tektonidou MG, Varsou N, Kotoulas G, Antoniou A, Moutopoulos HM. Cognitive deficits in patients with antiphospholipid syndrome: association with clinical, laboratory, and brain magnetic resonance imaging findings. Arch Intern Med. 2006;166(20):2278–84.
13. Chapman J, Cohen-Armon M, Shoenfeld Y, Korczyn A. Antiphospholipid antibodies permeabilize and depolarize brain synaptoneurosomes. Lupus. 1999;8(2):127–33.
14. Gertner E. Diffuse alveolar hemorrhage in the antiphospholipid syndrome: spectrum of disease and treatment. J Rheumatol. 1999.26(4):805–7.
15. Asherson RA, Cervera R, Wells AU. Diffuse alveolar hemorrhage: a non-thrombotic antiphospholipid lung syndrome? Semin Arthritis Rheum. 2006;35(3):138–42.
16. Deane KD, West SG. Antiphospholipid antibodies as a cause of pulmonary capillaritis and diffuse alveolar hemorrhage: a case series and literature review. Semin Arthritis Rheum. 2005;35(3):154–65.
17. Pierangeli SS, Girardi G, Vega-Ostertag M, Liu X, Espinola RG, et al. Requirement of activation of complement C3 and C5 for antiphospholipid antibody–mediated thrombophilia. Arthritis Rheum. 2005;52(7):2120–4.
18. Vega-Ostertag ME, Pierangeli SS. Mechanisms of aPL-mediated thrombosis: effects of aPL on endothelium and platelets. Curr Rheumatol Rep. 2007;9(3):190–7.
19. Oku K, Atsumi T, Boldogki M, Amengual O, Kataoka H, et al. Complement activation in patients with primary antiphospholipid syndrome. Ann Rheum Dis. 2009;68(6):1030–5.
20. Barratt-Due A, Fløisand Y, Orrem HL, Kvam AK, Holme PA, et al. Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. Rheumatology. 2016;55(7):1337–9.
21. Berman H, Rodríguez-Pintó I, Cervera R, Gregory S, de Meis E, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the “CAPS registry”. Autoimmun Rev. 2014;13(2):157–62.
22. Saañ SS, Patel YP, Desai A, Desai UR. Catastrophic antiphospholipid syndrome presenting as bilateral central retinal artery occlusions. Case Rep Ophthalmol Med. 2015. https://doi.org/10.1155/2015/206906.
23. Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, et al. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. Arch Ophthalmol. 1986;104(6):558–63.
24. Gold D, Feiner L, Henkind P. Retinal arterial occlusive disease in systemic lupus erythematosus. Arch Ophthalmol. 1977;95(9):1580–5.
25. Willis R, Pierangeli SS. Pathophysiology of the antiphospholipid antibody syndrome. Auto Immun Highlights. 2011;2(2):35–52.

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