An unusual case of multifocal central serous chorioretinopathy with low serum cortisol managed using eplerenone

Kanika Aggarwal, Aniruddha Agarwal, Vishali Gupta

In this report, we describe a rare case of a 44-year-old Asian male with acute central serous chorioretinopathy (CSC) with bullous exudative retinal detachment. Endocrinology evaluation revealed hypothalamic–pituitary–adrenal axis suppression with low serum cortisol. Furthermore, neuroimaging revealed the presence of a pituitary microadenoma. He was treated with systemic eplerenone and hydrocortisone. After 12 weeks, bullous detachment completely resolved. Our case is a unique description of acute CSC with underlying low serum cortisol levels that responded to treatment with mineralocorticoid antagonist. This case highlights the various endocrine abnormalities other than the raised serum cortisol that can occur in patients with CSC.

Key words: Cortisol, central serous chorioretinopathy, eplerenone, exudative retinal detachment, multifocal central serous chorioretinopathy

Till date, acute central serous chorioretinopathy (CSC) is a poorly understood condition characterized by retinal pigment epithelial (RPE) detachments, choroidal hyperpermeability with relative choriocapillaris hypoperfusion, and accumulation of subretinal fluid.[1,2] Excess of glucocorticoids (exogenous or endogenous) have been strongly linked with the pathogenesis of this condition.[3,4] Recently, a number of endocrinological abnormalities such as disruption of hypothalamic–pituitary–adrenal (HPA) axis, excessive endogenous glucocorticoids and mineralocorticoids, and renin–angiotensin–aldosterone pathway changes have been associated with the development of CSC.[5] However, development of CSC has not been reported among patients with low levels of endogenous glucocorticoids. In this report, we describe a unique case of a patient who developed a large, bullous exudative retinal detachment in the presence of low serum cortisol and suppressed HPA axis treated with oral eplerenone and paradoxically with oral hydrocortisone.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_651_18

Advanced Eye Center, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh, India

Correspondence to: Prof. Vishali Gupta, Advanced Eye Center, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh - 160 012, India. E-mail: vishalisara@yahoo.co.in

Manuscript received: 21.05.18; Revision accepted: 13.09.18

Cite this article as: Aggarwal K, Agarwal A, Gupta V. An unusual case of multifocal central serous chorioretinopathy with low serum cortisol managed using eplerenone. Indian J Ophthalmol 2019;67:167-70.

Case Report

A 44-year-old male presented with complaints of diminution of vision in both eyes (OU) of 15-day duration. He had history of similar complaints in the left eye (OS) 2 years back. He had been examined and was diagnosed with fibrinous CSC at another center. He had a history of using topical betamethasone ointment on the hands and feet for 1.5–2 years on a regular basis for skin allergy. He was advised to discontinue the use of topical steroids by the treating ophthalmologist followed by resolution of CSC in the OS within 6–8 weeks thereafter. However, on further questioning, he reported intermittent use of the steroid cream. He remained asymptomatic for 2 years before presenting to our center with similar visual complaints.

On examination, his best-corrected visual acuity (BCVA) was 6/9 in the right eye (OD) and 6/12 in OS. Slit-lamp biomicroscopic examination revealed the presence of multiple pockets of subretinal fluid in OU along with yellowish subretinal deposits and inferior exudative retinal detachment in OD [Fig. 1]. Fluorescein angiography showed multifocal leaks in early phase with pooling of the dye in the late-phase OU [Fig. 2]. In view of recurrent episodes of CSC, the patient was advised focal laser photocoagulation of the leaking points. The areas amenable to focal laser therapy away from the areas of subretinal fluid were treated. At the 6-week follow-up, the BCVA had further deteriorated to counting fingers at 3 m in OD and 6/24 in OS with worsening of exudative retinal detachment in OD [Fig. 3].

The patient was evaluated by an endocrinologist who advised systemic and laboratory work-up for pituitary hormones. Laboratory investigations revealed morning cortisol levels of 59.30 nmol/L (normal range: 171–536 nmol/L) and 76.53 nmol/L (on repeated testing) which were much below the normal physiological range. He also had low serum testosterone levels [9.64 nmol/L (normal range: 9.9–27.8) nmol/L], low serum T4 [3.86 μg/dL (normal range: 4.8–12.7 μg/dL)], and serum adrenocorticotropic hormone levels near the lower limit of normal [9.04 pg/mL (normal range: 5–60 pg/mL)]. The levels of prolactin [13.85 ng/L (normal range: 4–15.2 ng/L)], growth hormone [1.36 ng/mL (normal range: 0–2.50 ng/mL], luteinizing hormone [3.97 mIU/mL (normal range: 1.7–8.6 mIU/mL)], and follicle-stimulating hormone [4.8 mIU/mL (normal range: 1.5–12.4 mIU/mL)] were within normal range. The serum electrolytes were in the normal range. At this time, the patient was advised magnetic resonance imaging (MRI) of the brain to determine the presence of any pituitary lesion. MRI brain revealed a nodular lesion on the left side of the pituitary region (3.5 × 3.9 × 4.6 mm) (microadenoma). The endocrinologist opined that the microadenoma was possibly an incidental finding and it was nonfunctional. No active intervention was advised for the microadenoma. He was diagnosed to have HPA axis suppression which was attributed to the prolonged use of topical betamethasone ointment. In view of worsening exudative fluid in OU, the patient was started on oral eplerenone at a dose of 25 mg/day. The endocrinologist advised oral hydrocortisone 5 mg/day to maintain physiological levels of stress hormones needed to counter day-to-day stresses.

Following the initiation of oral eplerenone and hydrocortisone, the patient showed progressive improvement in BCVA with gradual decrease in the subretinal fluid, and slow but continuous resolution of the exudative retinal detachment in OD. At 3-month follow-up (after 6 weeks of therapy with oral eplerenone), his BCVA improved to 6/36 in OD and 6/18 in OS [Fig. 4].

At 6-month follow-up (after 12 weeks of therapy with oral eplerenone), his BCVA had improved to 6/24 (parts) in OD and 6/12 in OS with complete resolution of the exudative retinal detachment in OD and total resolution of subretinal fluid in OS [Fig. 5]. The endocrinologist has advised tapering of oral hydrocortisone based on the results of repeat laboratory hormone levels.

Discussion

The pathology of CSC involves development of serous retinal detachment, RPE abnormalities, choroidal hyperpermeability, and relative choriocapillaris ischemia because of a dysfunction involving the blood–retinal barriers and insufficient salt pumps at the RPE–Bruch's membrane.[1,3,6] Patients with an increase in endogenous corticosteroids in conditions such as Cushing's syndrome,[7] pregnancy,[8] and steroid producing tumors[9] also develop features of CSC, especially fibrinous type or with large bullous exudative retinal detachments.[10,11] Corticosteroid-related CSC can develop due to multifactorial effects of this hormone leading to increased RPE leakage, RPE cell apoptosis, and alterations in ion transport across RPE cells.[12]

While nearly 30% of patients may have HPA axis dysfunction with elevation of serum cortisol levels,[5,7] our patient demonstrated suppression of HPA axis and low serum cortisol levels along with other abnormalities such as low serum testosterone, which is unexpected in patients with CSC. It may be postulated that our patient developed HPA axis suppression after prolonged use of topical betamethasone ointment.[13] To maintain the normal levels of serum cortisol in the body to overcome day-to-day stresses, the patient was advised low physiological doses (5 mg) of oral hydrocortisone.

Our patient developed CSC because of possible exogenous corticosteroid exposure 2 years ago (before presentation to our center). Subsequently, due to intermittent corticosteroid ointment use, he developed HPA axis suppression leading to low levels of serum cortisol. The exact pathogenesis of CSC with low serum cortisol levels is unclear in our case. It is likely that CSC may occur as a result of myriad of endocrinological abnormalities including normal or low levels of serum cortisol. Thyroid-associated ophthalmopathy is well-known to occur in hypothyroid patients in 7.5% of cases, due to possible autoimmune mechanisms and other pathways which are not well-elucidated.[14,15] It may be possible that certain pathways, including *relative* mineralocorticoid excess, may lead to development of CSC in our patient.

Eplerenone, a mineralocorticoid antagonist, has been recently explored in the management of chronic CSC.[16] In the first published report of use of eplerenone by Zhao *et al*.,[17] 25 mg/day for 1 week followed by 50 mg/day led to rapid resolution of subretinal fluid and improvement in visual acuity. In a comparative study which included patients with bilateral chronic CSC with exudative retinal detachment in one eye and no exudative fluid in the fellow eye (n = 28),[18] treatment was initiated with 50 mg/day eplerenone for 3 months. There was a

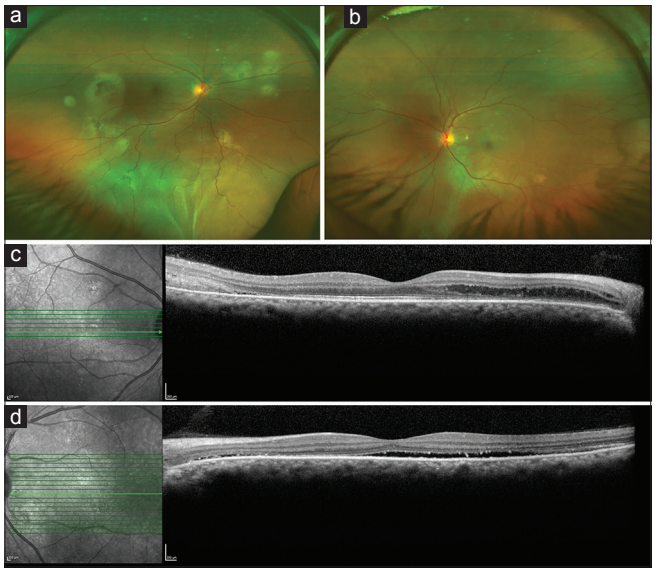

Figure 1: (a) Fundus photograph of the right eye showing multifocal areas of yellowish subretinal exudation with inferior exudative retinal detachment. (b) Fundus photograph of the left eye showing multiple variably sized grayish yellowish lesions with a loss of foveal transparency. (c) Optical coherence tomography line scan passing through macula of the right eye revealing outer retinal fluid nasally and subretinal hyperreflective deposits temporal to the fovea. (d) Optical coherence tomography line scan passing through the macula in the left eye showing the presence of a streak of subretinal fluid

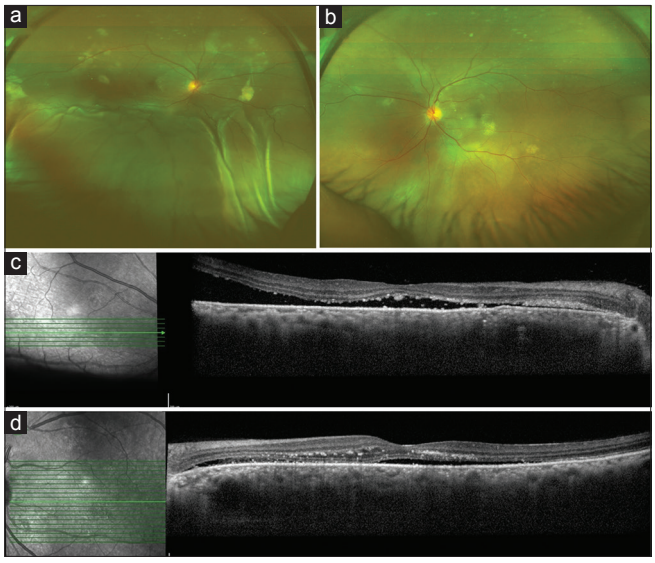

Figure 3: Follow-up at 6 weeks following focal laser treatment. (a) Fundus photograph of the right eye showing worsening of exudative detachment which had progressed to a bullous retinal detachment. (b) Fundus photograph of the left eye revealing pockets of subretinal fluid in the macular region. Optical coherence tomography line scan passing through the fovea showing increase in the subretinal fluid in the right (c) and the left eye (d)

significant decrease in the macular and choroidal thickness, and resolution of subretinal fluid at 6 months. The effect was more pronounced in the eye with exudative detachment, similar to our patient. A number of retrospective and prospective series on the use of eplerenone have been published since.[19-23]

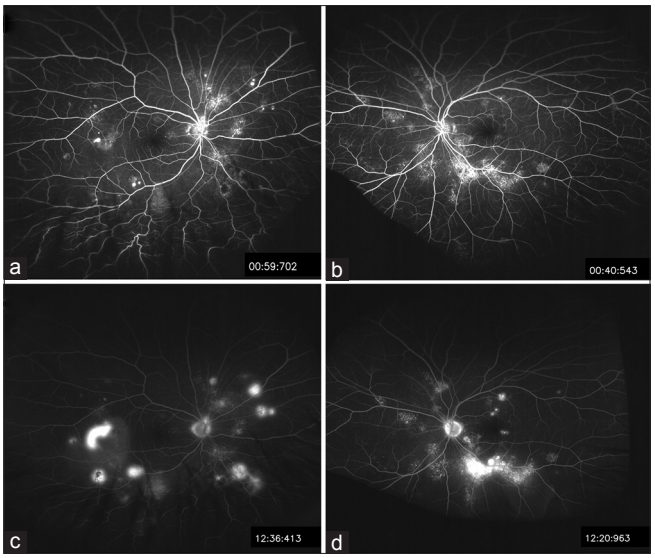

Figure 2: Fluorescein angiography (FA) at baseline. Early phase of FA revealing multiple hyperfluorescent dots with some areas of transmission hyperfluorescence in the right (a) and the left eye (b). Late phase of FA showing expanding dot sign and smoke-stack pattern in the right eye with pooling of the dye in the right eye (c) and expanding dot sign in the left eye as well (d)

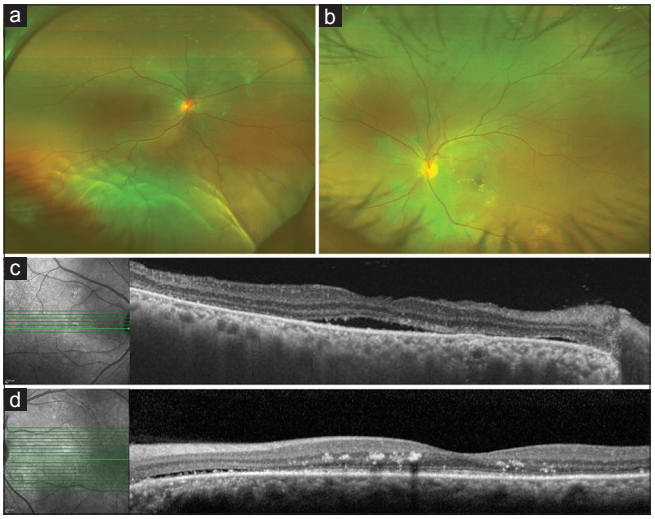

Figure 4: Follow-up after 6 weeks of therapy with oral eplerenone (25 mg once a day). Fundus photograph of the right eye showing significant resolution of the exudative retinal detachment (a) with improvement in the retinal transparency and appearance of yellowish subretinal precipitates in the left eye (b). Optical coherence tomography line scan passing through the fovea showing decrease in the subretinal fluid in the right (c) and the left eye (d)

The highlight of our case is the documentation of comprehensive hormonal profile which revealed low serum cortisol and other abnormalities. It may be possible to detect such abnormally low levels of cortisol in other cases of CSC if specifically investigated, especially among those patients who respond to eplerenone. Our case showed rapid and complete resolution of subretinal fluid within a period of 8–10 weeks with the help of eplerenone [Figs. 1 and 4]. From a stage where the retinal detachment was so bullous that even surgical intervention was considered [Fig. 3], our patient dramatically

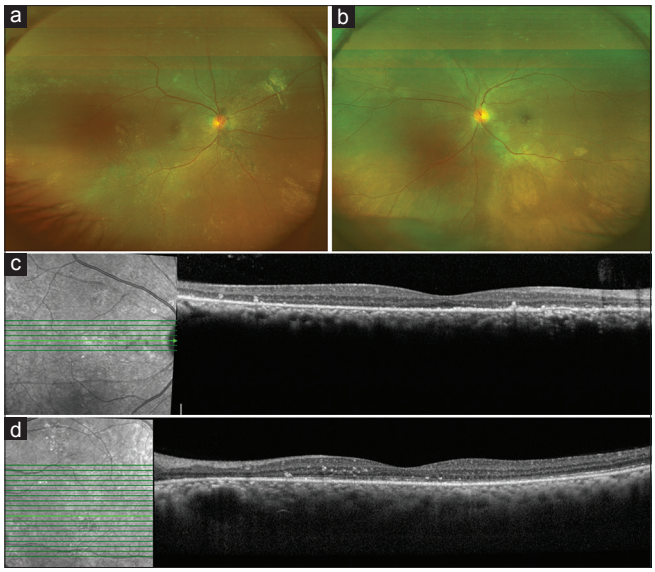

Figure 5: Follow-up after 12 weeks of therapy with oral eplerenone (25 mg once a day). Fundus photograph of the right eye shows complete resolution of the bullous exudative retinal detachment (a). Fundus photograph of the left eye (b) shows good retinal transparency and disappearance of the yellowish subretinal precipitates. Optical coherence tomography line scan passing through the fovea shows complete resolution of subretinal fluid in the right (c) and the left eye (OS) (d)

responded to only 25 mg/day eplerenone. While our case is able to successfully demonstrate the efficacy of eplerenone, it is very challenging to ascertain the pathophysiology of CSC with low serum cortisol based on our single case. It may be possible that a thorough investigation after pooling such cases, if any, may lead us to the pathogenesis of the disease in the future.

Conclusion

In summary, our case represents a rare association of CSC with low serum cortisol levels which responded to treatment with oral mineralocorticoid antagonist (eplerenone) along with physiological doses of hydrocortisone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 1967;63(Suppl):1-139.
2. Hussain D, Gass JD. Idiopathic central serous chorioretinopathy. Indian J Ophthalmol 1998;46:131-7.
3. Nicholson BP, Atchison E, Idris AA, Bakri SJ. Central serous chorioretinopathy and glucocorticoids: An update on evidence for association. Surv Ophthalmol 2018;63:1-8.
4. Farzan K, Rezaei L, Ghanbari H, Dehghani A. Central serous chorioretinopathy following kidney transplantation. Saudi J Kidney Dis Transpl 2014;25:615-20.
5. Haimovici R, Rumelt S, Melby J. Endocrine abnormalities in patients with central serous chorioretinopathy. Ophthalmology 2003;110:698-703.
6. Arndt C, Sari A, Ferre M, Parrat E, Courtas D, De Seze J, *et al.* Electrophysiological effects of corticosteroids on the retinal pigment epithelium. Invest Ophthalmol Vis Sci 2001;42:472-5.
7. Bouzas EA, Scott MH, Mastorakos G, Chrousos GP, Kaiser-Kupfer MI. Central serous chorioretinopathy in endogenous hypercortisolism. Arch Ophthalmol 1993;111:1229-33.
8. Chumbley LC, Frank RN. Central serous retinopathy and pregnancy. Am J Ophthalmol 1974;77:158-60.
9. Thoelen AM, Bernasconi PP, Schmid C, Messmer EP. Central serous chorioretinopathy associated with a carcinoma of the adrenal cortex. Retina 2000;20:98-9.
10. Rezai KA, Eliott D. Optical coherence tomographic findings in pregnancy-associated central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 2004;242:1014-6.
11. Parchand S, Gupta V, Gupta A, Dogra MR, Singh R, Sharma A. Dark spot in fibrinous central serous chorioretinopathy masquerading choroiditis. Ocul Immunol Inflamm 2013;21:201-6.
12. Yard AC, Kadowitz PJ. Studies on the mechanism of hydrocortisone potentiation of vasoconstrictor responses to epinephrine in the anesthetized animal. Eur J Pharmacol 1972;20:1-9.
13. Salde L, Lassus A. Systemic side-effects of three topical steroids in diseased skin. Curr Med Res Opin 1983;8:475-80.
14. Kashkouli MB, Pakdel F, Kiavash V, Heidari I, Heirati A, Jam S. Hyperthyroid vs hypothyroid eye disease: The same severity and activity. Eye 2011;25:1442-6.
15. Rajput R, Dhingra A, Kumar K, Sen J. Infiltrative ophthalmopathy and primary hypothyroidism: A rare clinical manifestation of a common disease. Postgrad Med J 2009;85:40-2.
16. Yang D, Eliott D. Systemic mineralocorticoid antagonists in the treatment of central serous chorioretinopathy. Semin Ophthalmol 2017;32:36-42.
17. Zhao M, Célérier I, Bousquet E, Jeanny JC, Jonet L, Savoldelli M, *et al.* Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. J Clin Invest 2012;122:2672-9.
18. Gergely R, Kovács I, Schneider M, Resch M, Papp A, Récsán Z, *et al.* Mineralocorticoid receptor antagonist treatment in bilateral chronic central serous chorioretinopathy: A comparative study of exudative and nonexudative fellow eyes. Retina 2017;37:1084-91.
19. Schwartz R, Habot-Wilner Z, Martinez MR, Nutman A, Goldenberg D, Cohen S, *et al.* Eplerenone for chronic central serous chorioretinopathy – A randomized controlled prospective study. Acta Ophthalmol 2017;95:e610-8.
20. Rahimy E, Pitcher JD 3rd, Hsu J, Adam MK, Shahlaee A, Samara WA, *et al.* A randomized double-blind placebo-control pilot study of eplerenone for the treatment of central serous chorioretinopathy (ECSELSIOR). Retina 2018;38:962-9.
21. Ghadiali Q, Jung JJ, Yu S, Patel SN, Yannuzzi LA. Central serous chorioretinopathy treated with mineralocorticoid antagonists: A one-year pilot study. Retina 2016;36:611-8.
22. Salz DA, Pitcher JD 3rd, Hsu J, Regillo CD, Fineman MS, Elliott KS, *et al.* Oral eplerenone for treatment of chronic central serous chorioretinopathy: A case series. Ophthalmic Surg Lasers Imaging Retina 2015;46:439-44.
23. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: A pilot study. Retina 2013;33:2096-102.