ASRS American Society of Retina Specialists

Journal of VitreoRetinal Diseases
2025, Vol. 9(4) 503–506

DOI: 10.1177/24741264251337104
journals.sagepub.com/home/jvrd
Sage

Bullous Central Serous Chorioretinopathy Associated With JAK Inhibitor Use

Warren Apel, MBBS, FRANZCO[1], and Ye Li, MBChB[1]

Abstract

Purpose: To report a case of bullous central serous chorioretinopathy (CSCR) after starting a Janus kinase (JAK) inhibitor and describe the results of focal laser treatment. **Methods:** A single case was evaluated. **Results:** A 54-year-old man with rheumatoid arthritis presented with a 2-week history of left superior field loss. His medications included prednisone 10 mg and upadacitinib, which was added to his regimen 3 weeks previously. His visual acuity (VA) was 20/25 OD and 20/30 OS. An ophthalmic examination of the left eye found an ill-defined white lesion of 2 × 3 disc diameters at the macula with an inferior retinal detachment (RD). Optical coherence tomography showed subretinal fibrin with subretinal fluid (SRF) and a pigment epithelial detachment. After a diagnosis of bullous CSCR was made, focal laser application was performed. One year later, the patient's VA recovered to 20/20 with resolved SRF. **Conclusions:** Bullous CSCR with a serous RD is an uncommon subtype of pachychoroid disease. Upadacitinib may be associated with its occurrence through disequilibrium of the coagulation cascade. Focal laser treatment offers a favorable outcome for this disease.

Keywords

bullous central serous chorioretinopathy, serous retinal detachment, focal laser

Introduction

Central serous chorioretinopathy (CSCR), characterized by an abnormally thickened choroid with choroidal vascular congestion, lies on the pachychoroid spectrum of chorioretinal disorders.[1] It is a common chorioretinopathy that manifests as a focal serous neurosensory retinal detachment (RD) secondary to choroidal venous congestion and retinal pigment epithelium (RPE) dysfunction. The serous RD is usually at the macula with accompanying features that frequently include choroidal thickening and pigment epithelial detachments (PEDs).[1]

CSCR is typically classified into acute, chronic, and recurrent based on the duration and resolution of subretinal fluid (SRF).[1] Acute cases are more likely to result in good visual outcomes. In contrast, chronic CSCR is more likely to be complicated by choroidal neovascularization, subretinal fibrin, and bullous RD.[1]

The bullous variant of CSCR is uncommon and is characterized by an extension of SRF beyond the vascular arcades with or without subretinal fibrin.[2] Because of its rare occurrence, the exact etiology of bullous CSCR is poorly understood; as a result, an optimal treatment regimen has yet to emerge.

We describe a rare case of fibrinous bullous CSCR in a patient with hypercortisolism who recently started a Janus kinase (JAK) inhibitor and responded well to focal laser application.

Case Report

A 54-year-old emmetropic White man presented with a 2-week history of painless left superior field loss. His medical history was significant for poorly controlled rheumatoid arthritis, for which he took long-term, low-dose oral prednisone 10 mg. Three weeks before the onset of symptoms, upadacitinib, a JAK inhibitor, was added to the patient's regimen. A physical examination was unremarkable. Of note, the patient had no ocular history.

On examination, the patient's visual acuity (VA) was 20/25 OD and 20/30 OS. An anterior segment examination was unremarkable. A fundus examination of the left eye showed an extrafoveal lesion of 2 × 3 disc diameters at the inferotemporal macula (Figure 1). The lesion was white with ill-defined borders. An associated inferior RD was present with peripheral extension beyond the inferotemporal vascular arcade to 4 clock hours. There were inferotemporal retinal hemorrhages with no

[1] Department of Ophthalmology, Sunshine Coast University Hospital, QLD, Australia

Corresponding Author:
Ye Li, Department of Ophthalmology, Sunshine Coast University Hospital, 6 Doherty St, Birtinya, QLD 4575, Australia.
Email: li.ye1210@gmail.com

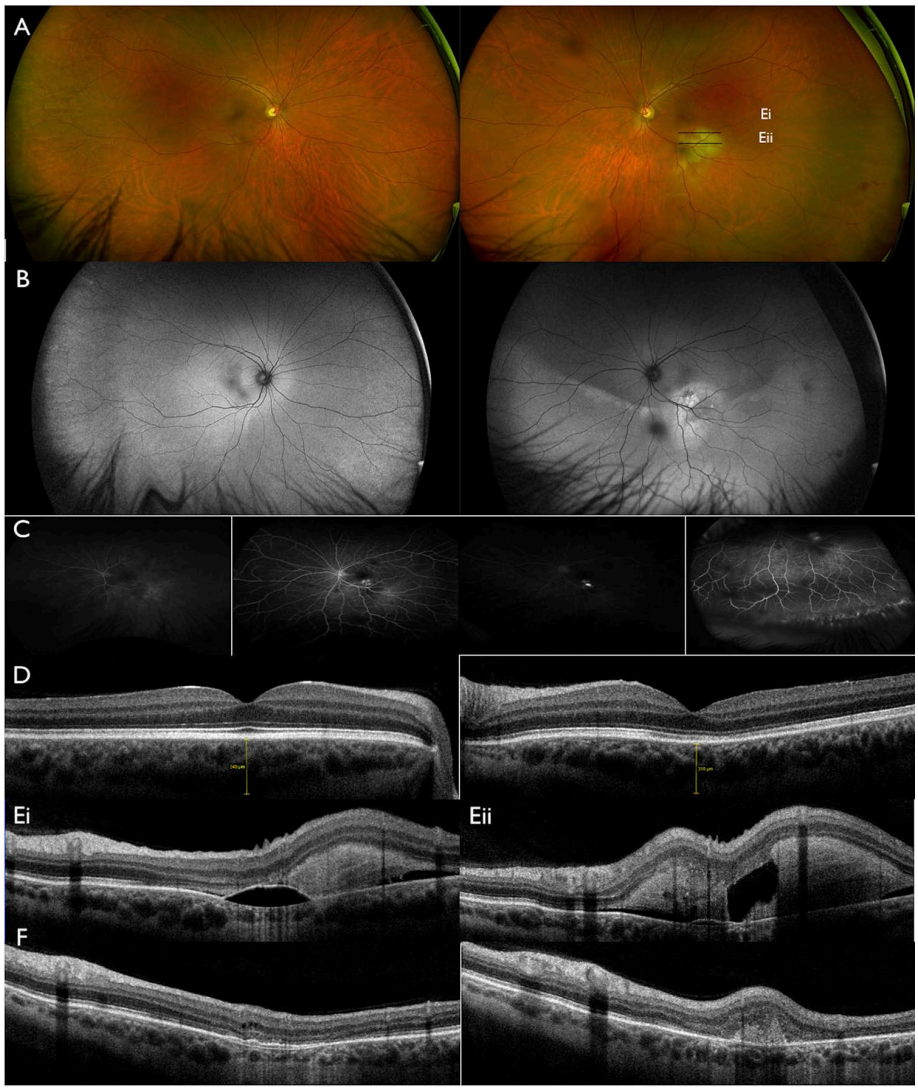

Figure 1. (A) Fundus photograph shows a white lesion of 2 × 3 disc diameters at the left inferotemporal macula that appears hyperautofluorescent on (B) fundus autofluorescence. (C) Fluorescein angiography shows multifocal leakage at the macula with peripheral nonperfusion. (D) Optical coherence tomography (OCT) shows increased subfoveal choroidal thickness in both eyes, 340 µm in the right eye and 310 µm in the left eye. (E) Abundant subretinal hyperreflective material and a large pigment epithelial detachment are also seen on OCT. (F) Five months after focal laser, there is near resolution of the subretinal fibrin with residual outer retinal atrophy in the left eye.

breaks. There was no associated vitritis, retinitis, or vasculitis. The examination of the right eye was unremarkable.

Optical coherence tomography (OCT) (Cirrus 6000, Carl Zeiss) showed increased subfoveal choroidal thickness in both eyes (Figure 1). In the left eye, there was extensive subretinal hyperreflective material at the inferotemporal macula with SRF, a small serous PED, and a thickened choroid. The inner retinal layers were preserved. Fundus autofluorescence (FAF) (Optos, Optos Inc) of the right eye showed gravitational hypoautofluorescence at the macula. FAF of the left eye showed RPE irregularity with punctate hyperautofluorescence at the macula and inferior hyperautofluorescence, suggesting a degree of chronicity (Figure 1). Fluorescein angiography (FA) of the left eye showed an area of pinpoint leakage stemming from the clinical lesion with peripheral nonperfusion (Figure 1).

Given the presence of unusual retinal changes in this immunosuppressed patient, an anterior chamber tap for herpes simplex virus 1 (HSV 1), HSV2, varicella-zoster virus, cytomegalovirus, and toxoplasmosis was performed to exclude viral retinitis. Serologic investigations, including the erythrocyte sedimentation rate, C-reactive protein, antineutrophil antibodies, antineutrophil cytoplasmic antibodies, angiotensin-converting enzyme, syphilis, and QuantiFERON Gold, were subsequently negative.

The patient was empirically treated with intravitreal foscarnet 0.1 mL (24 mg/mL) with oral valaciclovir 2 g 3 times daily. After a consultation with the rheumatologist, upadacitinib was

withheld because of the possibility of drug-induced reactions. After viral polymerase chain reaction testing returned negative, a likely diagnosis of fibrinous bullous CSCR was made.

The patient was encouraged to manage general risk factors, including stress, caffeine, and sleep. Treatment with photodynamic therapy (PDT) was considered but not possible as a result of the current worldwide shortage of verteporfin. Focal laser application comprising 9 shots × 100 μm × 100 ms × 200 mW was performed on the area of leakage as a temporizing measure because of an increase in symptoms and the risk for subfoveal involvement. Per a discussion with the rheumatologist, oral prednisone to remove exogenous corticosteroid drive could not be discontinued because of the possibility that the patient's already poorly controlled rheumatoid arthritis would worsen.

Sixteen months later, the patient's VA improved to 20/20, and symptomatic improvement was evident with reduced metamorphopsia and field recovery. OCT showed a reduction in SRF and subretinal fibrin with mild atrophy of the other retinal layers (Figure 1). Upadacitinib was changed to tocilizumab, and the patient remained on oral prednisone 10 mg to control his rheumatoid arthritis.

Conclusions

Bullous CSCR is a rare variant of CSCR that is often defined as a neurosensory detachment of the retina with more than 10 disc diameters of shifting SRF extending beyond the vascular arcades.[2,3] Whether bullous CSCR is a standalone entity to chronic CSCR is debatable given the many overlapping features.[4] Its diagnosis can often be difficult and it can be mistaken for other entities, such as infectious retinitis, posterior scleritis, and white-dot syndrome.[2,5,6] As outlined by Sahu et al,[6] management of bullous CSCR can be difficult because inflammatory chorioretinopathy must first be excluded, the treatment of which may in turn exacerbate CSCR's natural history.

Multimodal imaging can be useful to distinguish bullous CSCR from its masqueraders. Apart from the presence of an inferior exudative RD with increased choroidal thickness, pathognomonic phenotypic features of bullous CSCR are not well described because of the condition's infrequent occurrence.[2] In terms of exclusion of retinitis, the confinement of the yellow–white fibrinous lesions to the outer retinal layers can be a key differentiating feature.[6] Findings on FAF are variable, ranging from confluent hypoautofluorescence to granular hyperautofluorescence.[2] On OCT, unique features of bullous CSCR include turbid SRF, retinal folds, large PEDs, RPE tears, and hyperreflective subretinal fibrin.[2,4–6] Commonly shared features on FA include early hypofluorescence with multifocal leakage within the PEDs, telangiectasia of terminal capillaries, and peripheral nonperfusion within the bullous RD.

Kang et al[4] performed a large cohort study of 85 patients with chronic CSCR and 44 patients with bullous CSCR. The patients with bullous CSCR had a statistically significantly higher rate of turbid SRF, retinal folds, subretinal fibrin, multiple PEDs, RPE tears, submacular pachyvessels, choroidal hyperreflective spots, and the previously mentioned FA findings. It has been hypothesized that subretinal fibrin in the context of CSCR occurred secondary to the entrance of fibrin through PEDs, which were seen in our patient.

The presence of fibrin was thought to mediate a cascade of anatomic changes to the outer retina and choroid, resulting in an exudative RD.[2] In addition, Kang et al[4] believe that the accumulation of fibrin resulted from the inhibition of fibrinolytic pathways through excess hypercortisolism, causing an amplified exudative response that ultimately leads to a bullous detachment.

The role of subretinal fibrin in our patient's case may pose an interesting link between the recent initiation of upadacitinib, a JAK inhibitor, to the onset of symptoms. Despite promising disease-modifying results in rheumatoid arthritis,[7] a notable side effect of JAK inhibitors is the increased risk for thromboembolism through a mechanism that has yet to be elucidated. It has been postulated that there may be interactions between the JAK signaling pathway, cytokines, and prothrombotic factors that disrupt the equilibrium between fibrinolysis and coagulation, resulting in thrombosis.[8] Changes in systemic vasculature can be extrapolated to choroidal vasculature, the physiology of which may also be affected by JAK inhibition in a similar manner.

Fibrin is an enabling component of the thrombotic cascade. Although there is no clear link between changes in the thromboembolic cascade and fibrin deposition, the recent introduction of upadacitinib may be the catalyst in the observed exponential rise in subretinal fibrin. This may have resulted in increased exudation and bullous detachment in this patient with preexisting asymptomatic choroidal venous congestion from long-term corticosteroid use. This may indeed have been the second hit in the 2-hit model of CSCR manifestation, where the first hit from choroidal venous overload is propagated by the second hit from elements such as fibrin accumulation, corticosteroid excess, and choroidal endothelial cell dysfunction.[4] In phase 3 trials of upadacitinib, 2 cases of RD were reported; however, those patients had other risk factors for RD, and no further clinical information is available.[9]

It is also possible that CSCR occurred secondary to corticosteroid excess from long-term prednisone use alone. However, its timely onset after starting upadacitinib may not be a coincidence, and the lack of recurrence after ongoing prednisone use suggests otherwise. Interestingly, Kang et al[4] noted a higher, but not statistically significant, proportion of patients treated with immunomodulatory therapy in the bullous CSCR group than the chronic CSCR group. Although the type of immunomodulatory therapy used was not specified, the presence of JAK inhibitor use in this group would be interesting to ascertain because this may help establish a potential link between its use and the development of bullous CSCR.

Many tools are available in the armamentarium of treatment options for CSCR; however, a gold standard for the bullous variant has yet to emerge. Although cessation of the root cause, corticosteroids, is certainly recommended, systemic comorbidities, such as those seen in our patient, may present obstacles. Previous case series have described options including observation, antivascular endothelial growth factor, PDT, and focal laser application.[2,4–6,10] Current case studies have reported variability in terms of treatment, likely reflecting management on a case-by-case basis and an undefined treatment regimen.

We acknowledge the limitations of this case report. It is possible that the combination of JAK inhibition and long-term corticosteroid use contributed to the manifestation of bullous CSCR in this patient; however, the exact mechanism is unknown. Because of the duration of the follow-up, we were unable to determine the long-term effect of focal laser use in silencing disease activity, outer retinal atrophy, and subretinal fibrosis.

In conclusion, a patient's clinical history and multimodal imaging can assist with the diagnosis of bullous CSCR. As an uncommon variant of CSCR, diagnostic uncertainty may often arise, in particular in the context of immunosuppressed and medically complex patients who are at risk because of other causes. In such situations, the initial exclusion of infectious and inflammatory differentials that may threaten the sight is necessary. Although further evidence is required to determine whether a relationship exists between JAK inhibitors and bullous CSCR, patients with preexisting susceptibility to CSCR should be counseled regarding its potential development when starting medications that may impede fibrinolysis, choroidal endothelial cell function, or the RPE pump. In this patient's case, discontinuation of the JAK inhibitor and the use of a focal laser were effective, resulting in a reduction in SRF and an improvement in visual function.

Ethical Approval

This case report was exempt from institutional review board approval.

Statement of Informed Consent

The patient provided verbal informed consent, including permission for publication of his information and the images included herein.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Ye Li https://orcid.org/0000-0002-4585-956X

References

1. Cheung CMG, Lee WK, Koizumi H, Dansingani K, Lai TYY, Freund KB. Pachychoroid disease. *Eye (Lond)*. 2019;33(1):14-33. doi:10.1038/s41433-018-0158-4
2. Balaratnasingam C, Freund KB, Tan AM, et al. Bullous variant of central serous chorioretinopathy: expansion of phenotypic features using multimethod imaging. *Ophthalmology*. 2016;123(7):1541-1552. doi:10.1016/j.ophtha.2016.03.017
3. Gass JD. Bullous retinal detachment. An unusual manifestation of idiopathic central serous choroidopathy. *Am J Ophthalmol*. 1973;75(5):810-821. doi:10.1016/0002-9394(73)90887-8
4. Kang HG, Woo SJ, Lee JY, et al. Pathogenic risk factors and associated outcomes in the bullous variant of central serous chorioretinopathy. *Ophthalmol Retina*. 2022;6(10):939-948. doi:10.1016/j.oret.2022.04.015
5. Cebeci Z, Oray M, Bayraktar Ş, Tuğal-Tutkun İ, Kır N. Atypical central serous chorioretinopathy. *Turk J Ophthalmol*. 2017;47(4):238-242. doi:10.4274/tjo.38039
6. Sahu DK, Namperumalsamy P, Hilton GF, de Sousa NF. Bullous variant of idiopathic central serous chorioretinopathy. *Br J Ophthalmol*. 2000;84(5):485-492. doi:10.1136/bjo.84.5.485
7. Mori S, Ogata F, Tsunoda R. Risk of venous thromboembolism associated with Janus kinase inhibitors for rheumatoid arthritis: case presentation and literature review. *Clin Rheumatol*. 2021;40(11):4457-4471. doi:10.1007/s10067-021-05911-4
8. Kotyla PJ, Engelmann M, Giemza-Stokłosa J, Wnuk B, Islam MA. Thromboembolic adverse drug reactions in Janus kinase (JAK) inhibitors: does the inhibitor specificity play a role? *Int J Mol Sci*. 2021;22(5):2449. doi:10.3390/ijms22052449
9. Guttman-Yassky E, Thyssen JP, Silverberg JI, et al. Safety of upadacitinib in moderate-to-severe atopic dermatitis: an integrated analysis of phase 3 studies. *J Allergy Clin Immunol*. 2023;151(1):172-181. doi:10.1016/j.jaci.2022.09.023
10. Anderson WJ, Smith BT. Bilateral bullous central serous chorioretinopathy treated with PDT and eplerenone. *Am J Ophthalmol Case Rep*. 2022;28:101739. doi:10.1016/j.ajoc.2022.101739