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Case of the Month – November 2019

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A 47-year-old white male presented with complaints of decreased vision in his left eye (OS). He characterized the vision loss as sudden in onset, with a "warped" quality within his central visual axis and extending superiorly. He had a lifelong history of poor vision in the right eye (OD), from anisometropic amblyopia and felt his vision was stable in that eye. He reported a history of hypertension, well controlled on oral losartan.

Visual acuity (VA) was 20/150 ph 20/80 in the OD and 20/60 phni in the OS. Intraocular pressures and anterior segment exam were normal. Dilated fundus exam revealed a focal, small retinal pigment epithelial detachment (PED) in the OD and a large PED with extensive subretinal fluid (SRF) in the OS (Figures 1A-B). Optical coherence tomography (OCT) conveyed fibrinous subretinal exudates overlying an oblong, flat PED OS (Figures 1D for OD; 1E-G for OS). Fluorescein angiography (FA) revealed hyperfluorescent pooling in the PED OD, contrasted with a hyperfluorescent smokestack pattern OS.

Clinical Course:

The findings and diagnosis of central serous chorioretinopathy (CSCR) were explained to the patient. The natural history of the disease and treatment options, including close monitoring, photodynamic therapy, oral eplerenone, oral rifampin, and intravitreal anti-VEGF therapy were discussed. He elected to proceed with oral eplerenone complemented by mindfulness-based stress reduction with a psychologist. Corticosteroid avoidance was recommended. He denied use of prescribed or over-the-counter steroids, including inhalers or creams.

Two weeks after starting Eplerenone 50 mg PO daily, VA improved to 20/40 OS, with a significant reduction in SRF. Labs (including potassium) were normal and blood pressure was at target, per his PCP. During the third week of treatment, he developed dizziness and hypotension. It was discovered that he had been restricting his fluid intake to "avoid fluid buildup." He was reassured that fluid intake wouldn't worsen CSCR. Electrolyte intake was encouraged. Losartan was held by his PCP. The dizziness resolved without recurrence.

Six weeks after initiating treatment, vision improved to 20/25 OS with near complete resolution of SRF (Figure 2). The patient was given instructions to continue at the current dose of Eplerenone 50 mg PO daily, with a plan to reduce the dose to 25 mg daily upon complete resolution of SRF.

Discussion:

Central serous chorioretinopathy, first described in 1866 by Dr. Albrecht von Graefe (who named it central recurrent retinitis), is a chorioretinal disease of multifactorial etiology. It is characterized by the accumulation of SRF and PEDs, leading to decreased vision, micropsia, metamorphopsia, or paracentral scotoma. CSCR typically affects patients aged 25-55, and is about 6 times more common in males. The incidence is 9.9 per 100,000 in men (and up to 18.3 per 100,000 in active service military). It is more common in Caucasians, Asians, and Latinos than in African Americans. The most important risk factors for the disease are related to stress: high exogenous or endogenous corticosteroid levels. Obstructive sleep apnea, type A personality, *Helicobacter pylori*, collagen vascular disease, and hypertension have also been implicated as risk factors for CSCR. The disease nomenclature was reclassified multiple times in the 20th century.

Early proposed mechanisms of CSCR included retinal vessel spasm, which was debunked by FA and replaced with a theory of RPE dysfunction – an incompetent RPE that was unable to "hold back" SRF. Today, the choroid and choriocapillaris are implicated as the initial foci of the disease, with an ineffective RPE thought to play a secondary role. Hyperdynamic choroidal circulation and choroidal hyperpermeability (demonstrated by indocyanine green angiography) and impaired RPE function is thought to lead to fluid pooling in the sub-RPE space. This leads to leakage through the RPE tight junctions into the subretinal space and neurosensory detachment. Several studies have demonstrated a thickened choroid. With prolonged periods of SRF leading to loss of photoreceptor outer segment interdigitation with the apices of the RPE, there is loss of visual function, chronic RPE changes, and atrophy.

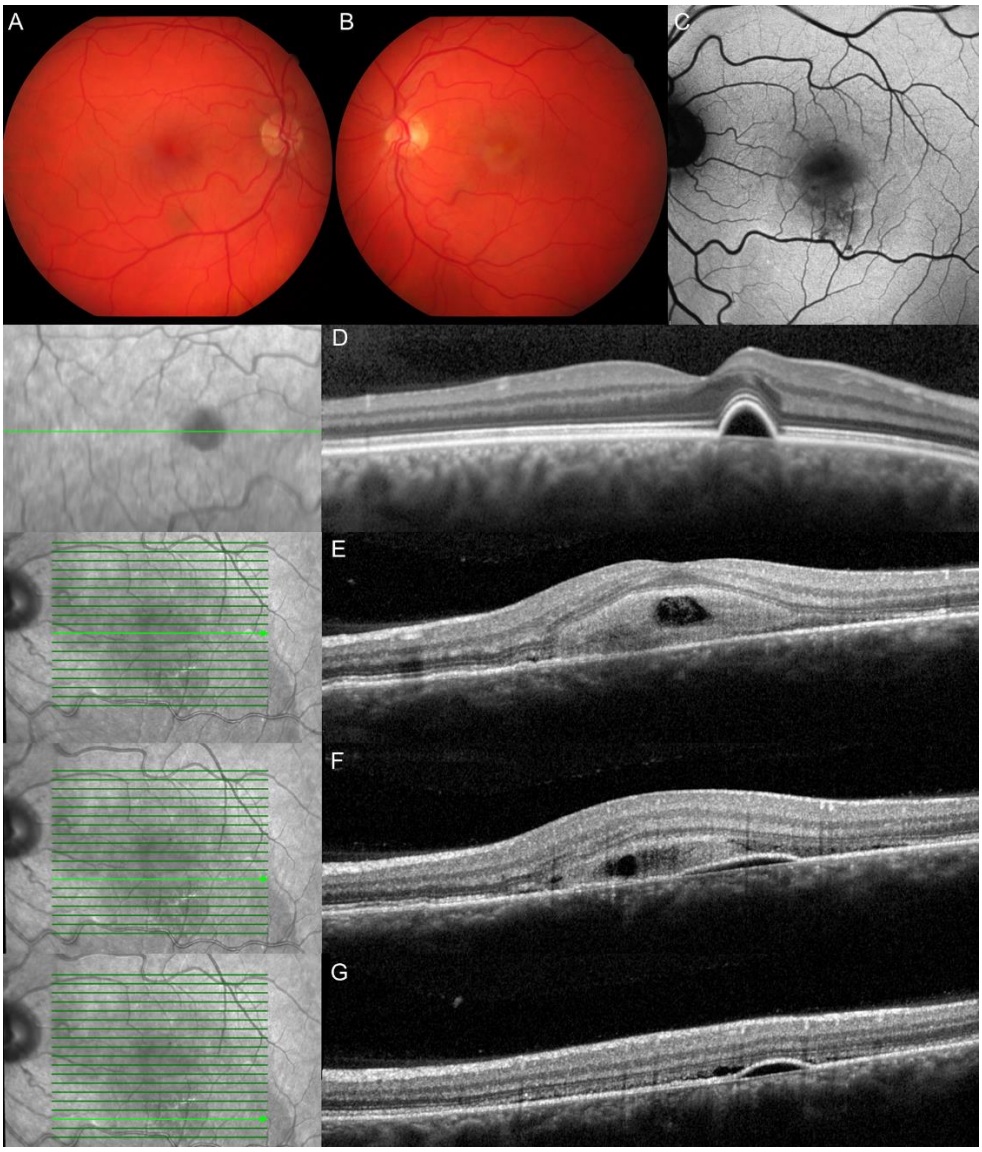

Figure 1: (A) Color fundus photography revealed focal PED in the right eye, and (B) fibrinous subretinal fluid overlying a PED in the left eye. (C) Autofluorescence of the left eye revealed mild hypoautofluorescence from subretinal fluid and focal, dense, hypoautofluorescence due to early RPE changes. (D) Optical coherence tomography (OCT) of the right eye showed focal PED perifoveally. (E-G) Meanwhile, OCT of the left eye showed extensive fibrinous subretinal exudate and fluid overlying a flat, oblong PED, leading to loss of the foveal contour.

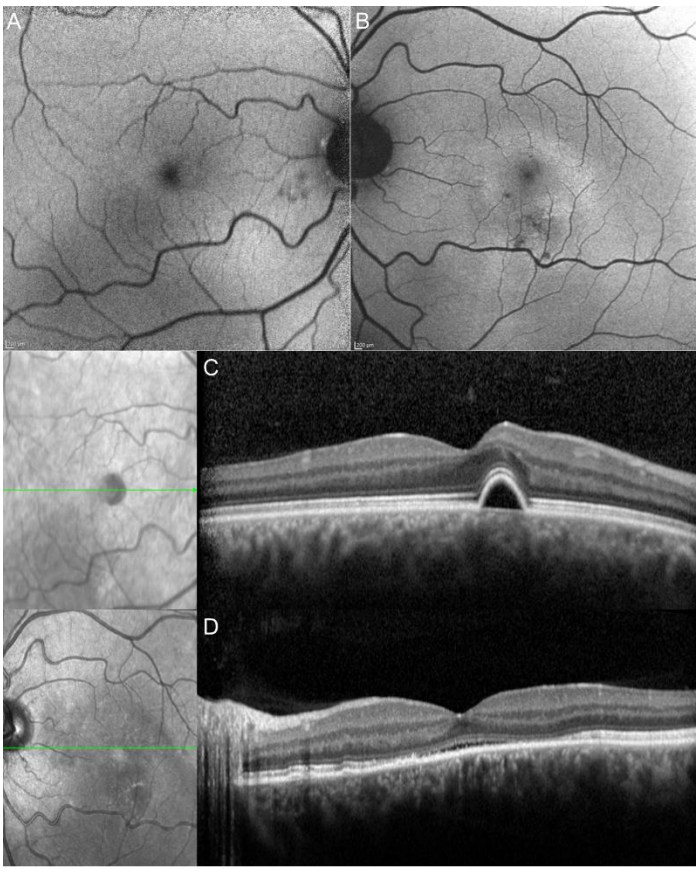

Figure 2: (A) Autofluorescence of the right eye 6 weeks after initiating treatment conveyed focal, mild, perifoveal hyperautofluorescence corresponding to the PED. (B) The left eye demonstrated near resolution of the hypoautofluorescent SRF, replaced now by a subtle, perifoveal ring of hyperautofluorescence. (C) Optical coherence tomography of the right eye showed a stable perifoveal PED. (D) OCT of the left eye showed marked improvement, with near complete resolution of subretinal fluid and persistent subfoveal ellipsoid zone band discontinuity and RPE changes.

The prognosis of patients with CSCR is associated with presenting visual acuity. Patients often present with bilateral, albeit asymmetric findings. The majority of primary cases (80-90%) are expected to resolve spontaneously within 3 to 4 months and visual improvement may lag anatomic recovery. Up to 50% of patients will experience a recurrent episode, often within 1 year of the incipient event. Patients with chronic CSCR may have distinctive RPE changes and persistent shallow, serous retinal detachments or extramacular RPE atrophy.

Elevated exogenous or endogenous corticosteroid levels are the greatest risk factor for CSCR. Meticulous questioning is required – for example, patients periodically using an inhaled corticosteroid or over-the-counter steroid ointment – may not recall steroid use unless specifically asked. When possible, the steroid should be stopped. Steroids have also been shown to lead to an increase in vascular permeability, and they may reverse RPE cell polarity, leading to the pumping of ions subretinally, followed by SRF. In one study, 100% of patients had resolution of SRF after corticosteroid cessation, compared to 88% in a second.

Some have argued for an association between obstructive sleep apnea (OSA) and CSCR. Postulated mechanisms have included increased catecholamines, oxidative stress, vasoconstriction, and blood coagulation abnormalities in patients with OSA. In one study, 22% of patients were found to have OSA via sleep study, after having a positive Epworth Sleepiness Scale survey (n=36). In another prospective, case control study, 48 patients with CSCR (and no history of steroid use) were matched with controls for age, gender, body mass index, diabetes, and hypertension. There was no difference in OSA risk (45.8% vs 43.8%) between the two groups.

In 1987, Dr. Yannuzzi noted an association between CSCR and Type A behavioral pattern (Type A personality). Patients with CSCR and case-matched controls were given the Jenkins Activity Survey, which consisted of 52 weighted questions assessing: Factor-S (speed and impatience), Factor-H (hard driving and competitive), and Factor-J (job involvement). Scores in the top third classified as type A. Sub-analysis showed that Factor-S was more strongly linked to CSCR, Factor-H to a lesser degree, and there was no difference in Factor-J scores. Other possible risk factors for CSCR include *Helicobacter pylori*, erectile dysfunction, exogenous testosterone, hypertension, psychopharmacologic medications, and coronary heart disease.

Ancillary diagnostic testing can be helpful in establishing the diagnosis of CSCR, in predicting the prognosis, and in monitoring the response to treatment. Subtle SRF may not be evident on clinical examination without the aid of contact-lens biomicroscopy, and OCT can be helpful for monitoring the resorption of SRF with treatment. Small PEDs within the pocket of SRF on OCT, in a patient of the anticipated demographic, are fairly pathognomonic for CSCR. Enhanced-depth imaging OCT can be used to measure choroidal thickness, which is typically larger than average.

Autofluorescence is helpful for monitoring chronic changes in the disease, with outer retinal and RPE atrophy. RPE hypoautofluorescence is seen corresponding to the distribution of SRF, as the overlying SRF prevents transmission of the RPE. “Guttering” is a common, albeit non-specific, finding in CSCR - troughs of fluid that have chronically lingered adopt a gravity-dependent distribution (red arrow; Figure 3).

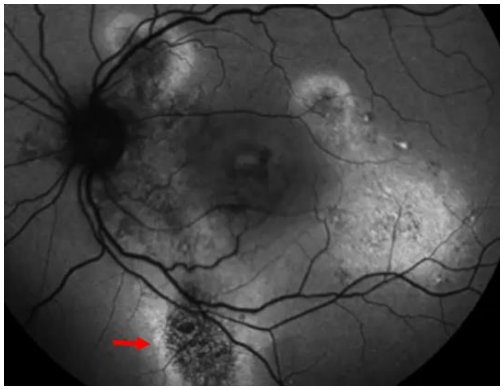

Figure 3: Autofluorescence shows many hyperautofluorescent patches consistent with RPE changes and guttering inferiorly (red arrow), consistent with chronic, gravity-dependent subretinal fluid.

Fluorescein angiography and indocyanine green angiography can be helpful in making the diagnosis. An “expansile dot pattern” is most commonly seen on FA, whereby a small, focal, hyperfluorescent leak from the choroid through RPE is noted early, followed by expanding hyperfluorescence later. A “smokestack pattern” on FA can be seen in about 10% of cases (Figures 4A-B). This pattern starts as a central spot that spreads vertically, then laterally, secondary to convection currents – a pressure gradient between protein concentration of subretinal fluid and fluorescein dye entering neurosensory detachment. A third, “diffuse” FA pattern is rare. Indocyanine green angiography (ICGA) can be helpful to elucidate choroidal vascular abnormalities, including hyperdynamic choroidal circulation and choroidal hyperpermeability, typically seen on early phases. Other features on ICGA can include filling delays in choroidal arteries, venous dilation, and multifocal choroidal hyperfluorescent patches.

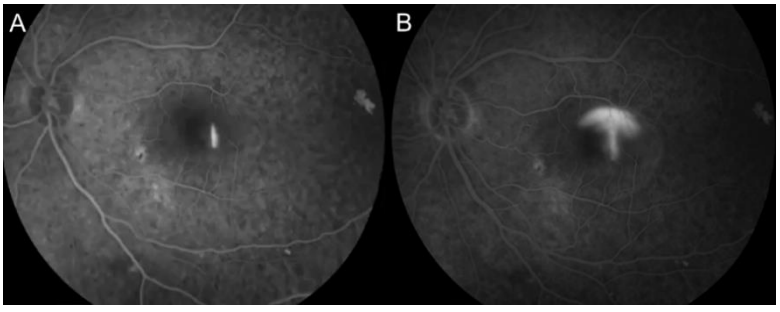

Figure 4: (A) Fluorescein angiography conveys early, pinpoint hyperfluorescent leakage, followed by (B) an expansion in vertical and horizontal area of hyperfluorescence in the late phase known as a “smokestack appearance.”

The treatment of CSCR is both a science and art, with multiple treatment options. Management should be tailored to the individual patient. An initial, acute episode of CSCR can be self-limiting in 80-90% of cases. Assuming a binocular patient with unilateral pathology, close monitoring may be a good initial option.

Photodynamic therapy (PDT) with verteporfin (typically half-fluence 300 mW/cm^2 for 83 seconds at 25 J/cm^3 versus full-fluence 600 mW/cm^2 with reduced time) can be particularly efficacious for unifocal disease, or when the pathology can be captured within the PDT spot size. It is thought to help by reinforcing the blood-retinal barrier. One study showed resolution of SRF in 93.4% of patients with CSCR that were treated with PDT. A second study, found resolution of SRF after PDT in 97% of cases without recurrence (n=67). Limitations of PDT include the need for intravenous access, a trained nurse, possible scotoma, and need for sunlight-avoidance.

Oral rifampin (300 or 600 mg daily) has shown efficacy in some patients. It is postulated to work by inducing cytochrome P450 3A4 to metabolize and reduce endogenous corticosteroids. The first case report of rifampin for the treatment of CSCR was in 2012 in a patient who also had tuberculosis. Side effects can include flu-like symptoms, hepatotoxicity, rashes, and GI intolerance. Rifampin may decrease the efficacy of steroids otherwise needed by the patient (e.g. to prevent a transplant rejection or for a systemic autoimmune condition).

Oral eplerenone (50 mg daily) has also been shown to have good efficacy. It can be particularly useful in bilateral and multifocal cases. It is postulated to work via antagonism of mineralocorticoid receptors. These receptors, in the absence of antagonism, would allow corticosteroid binding to trigger choroidal vasodilation. The risks of treatment with systemic eplerenone include hyperkalemia (especially in diabetes or renal failure) or hypotension and/or dizziness. It is important to work closely with the patient's primary care physician.

Intravitreal anti-vascular endothelial growth factor injections – e.g. bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea) – may also have a role in the treatment of CSCR. The CONTAIN study assessed the response of 12 patients to monthly intravitreal Eylea over 6 months. Pre-treatment mean VA was 62 ETDRS letters, compared to post-treatment mean VA of 64 letters (p=0.56). Six of 12 (50%) had resolution of subretinal fluid; mean central macular thickness improved from 400 to 306 μm (p=0.03), mean subfoveal fluid from 159 to 49 μm (p=0.02), and mean choroidal thickness decreased from 307 to 263 μm (p=0.0003).

Finally, both at the molecular basis (e.g. mineralocorticoid receptors) and the cognitive level (e.g. Type A personality), stress is highly implicated in CSCR. It is helpful to ask patients about stress in their personal or work life and gauge their interest in partnering with a professional skilled in stress reduction. A mental health professional can teach skills of cognitive behavioral therapy, mindfulness meditation, or other stress-reduction techniques, which may help the patient better manage his or her disease burden.

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Take Home Points: Central Serous Chorioretinopathy

- Subretinal fluid overlying a retinal pigment epithelial detachment is highly specific for CSCR.
- Multimodal imaging can help establish the diagnosis and monitor response to treatment.
- Ask patients about steroid use (e.g. creams & inhalers). If possible, stop all corticosteroids.
- Most acute cases resolve spontaneously. Treatment should be customized to the patient.


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