Spontaneous resolution of chronic central serous chorioretinopathy: "Fuji Sign"

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Reports

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Central serous chorioretinopathy (CSC) is a common chorioretinal disease that is characterized by the presence of subretinal fluid (SRF) in the macula.[1] It is traditionally classified into 2 main subtypes, acute CSC and chronic CSC (cCSC), with the latter typically having persistent SRF, which leads to retinal damage and, ultimately, impaired visual function.[2] Interestingly, in the Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI) trial, as many as 30% of the placebo-treated patients with cCSC had a complete resolution of SRF after 12 months, indicating that spontaneous SRF resolution may occur both in acute CSC and—to a lesser extent—cCSC.[3] This raises the question of whether there are clinical signs that could help determine which patients may experience such spontaneous SRF resolution. Therefore, the current study describes the clinical characteristics and findings on multimodal imaging of patients with cCSC in whom spontaneous SRF resolution occurred and introduces the "Fuji sign" as a novel morphologic feature on OCT that is strongly associated with a higher likelihood of spontaneous SRF resolution.

This retrospective, multicenter cohort study included adult, treatment-naïve patients with cCSC in whom spontaneous SRF resolution occurred between 2013 and 2021 and defined characteristic findings of cCSC on fluorescein angiography (FA), indocyanine green angiography, and fundus autofluorescence. Data were obtained from the following 3 academic medical centers: Leiden University Medical Center (the Netherlands), Amsterdam University Medical Centers (the Netherlands), and Oxford University Hospitals National Health Service Foundation Trust (United Kingdom). The study adhered to the tenets of the Declaration of Helsinki, and institutional review board/ethics committee approval (Medical Ethics Committee Leiden, The Hague and Delft) and informed consent from all patients were obtained before the start of the study.

In our experience, in clinical practice, spontaneous SRF resolution occurred more commonly in patients with a morphologic feature that we describe as the "Fuji sign." This is present when the shape of the SRF, on OCT, resembles the summit of Mount Fuji in Japan before spontaneous SRF resolution (Fig 1 and Fig S1, available at www.ophthalmologyretina.org). Therefore, the primary outcome measure of this study was the presence of the Fuji sign at the patients' baseline visit (the first visit at the medical center during which an active episode of cCSC was diagnosed with the presence of SRF under the foveola). For a patient to be included in the study, spontaneous resolution must have occurred at the first follow-up visit (after the baseline visit). To determine the presence of the Fuji sign, first, on a foveal horizontal OCT scan, a line was drawn from the innermost part of the ellipsoid zone to the Bruch membrane (Fig 1). The base of the triangle was drawn halfway and perpendicular to this line. The 2 legs of the triangle were drawn from the external limiting membrane, at the apex of the SRF, to the 2 points where the baseline intersected with the external limiting membrane. The Fuji sign was considered to be present when the external limiting membrane was positioned either exactly overlapping the 2 legs of the triangle or under these lines (often in a concave shape; Fig 1). In some cases the SRF had steep angles at both ends, as also described in age-related macular degeneration, and thus did not meet the Fuji sign criteria, despite the predominantly concave shape of the external limiting membrane (Fig 1A).[7] In view of this, the baseline of the triangle was not located on Bruch's membrane, but instead halfway between the ellipsoid zone and the Bruch's membrane to optimally assess the presence of the Fuji sign.

The second main outcome measure was the number of focal leakage points on FA at the baseline visit. Other characteristics on FA, indocyanine green angiography, and OCT that were documented at the baseline visit are summarized in Table S1 (available at www.ophthalmologyretina.org).

Age-matched and sex-matched controls were selected out of the Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy (PLACE) and Half-Dose Photodynamic Therapy Versus Eplerenone in Chronic Central Serous Chorioretinopathy (SPECTRA) randomized controlled treatment trials, in which treatment-naïve patients with cCSC received treatment shortly after the baseline visit.[4,5] All imaging was graded by 2 independent graders (H.M.A.F. and J.H.), with a third retina specialist (E.H.C.v.D.) involved in case of disagreement.

This study included 76 patients with cCSC (38 in each group), for whom the baseline characteristics can be found in Table S1. The Fuji sign was observed significantly more frequently on OCT in the study group than in the control group (16 out of 38 [42.1%] and 5 out of 38 [3.2%], respectively; $P = 0.005$). There was substantial interobserver agreement (κ, 0.633; 95% CI, 0.435−0.831; $P < 0.001$). The number of focal leakage points on FA were significantly higher in the control group than in the study group (1.8 ± 1.0 [n = 37] and 0.8 ± 0.7 [n = 23], respectively; $P < 0.001$).

The median time between baseline and the visit after spontaneous SRF resolution was 3.0 months (range, 0.2−14.8 months). The clinical and multimodal imaging characteristics of the study patients during follow-up are summarized in Table S2 (available at www.ophthalmologyretina.org). During further follow-up of the study group patients after a median of 21.0 months (range, 4.3−61.1 months), 8 out of 18 (44.4%) patients experienced recurrence.

Our results suggest that the Fuji sign can help distinguish which patients with cCSC have a higher chance of spontaneous SRF resolution without treatment and may, therefore, be suitable for an active monitoring approach. This is particularly relevant because there is currently a worldwide shortage of verteporfin, and verteporfin-assisted photodynamic therapy is a costly treatment. However, to avoid irreversible photoreceptor damage because of long-standing persistent SRF despite the Fuji sign, a follow-up

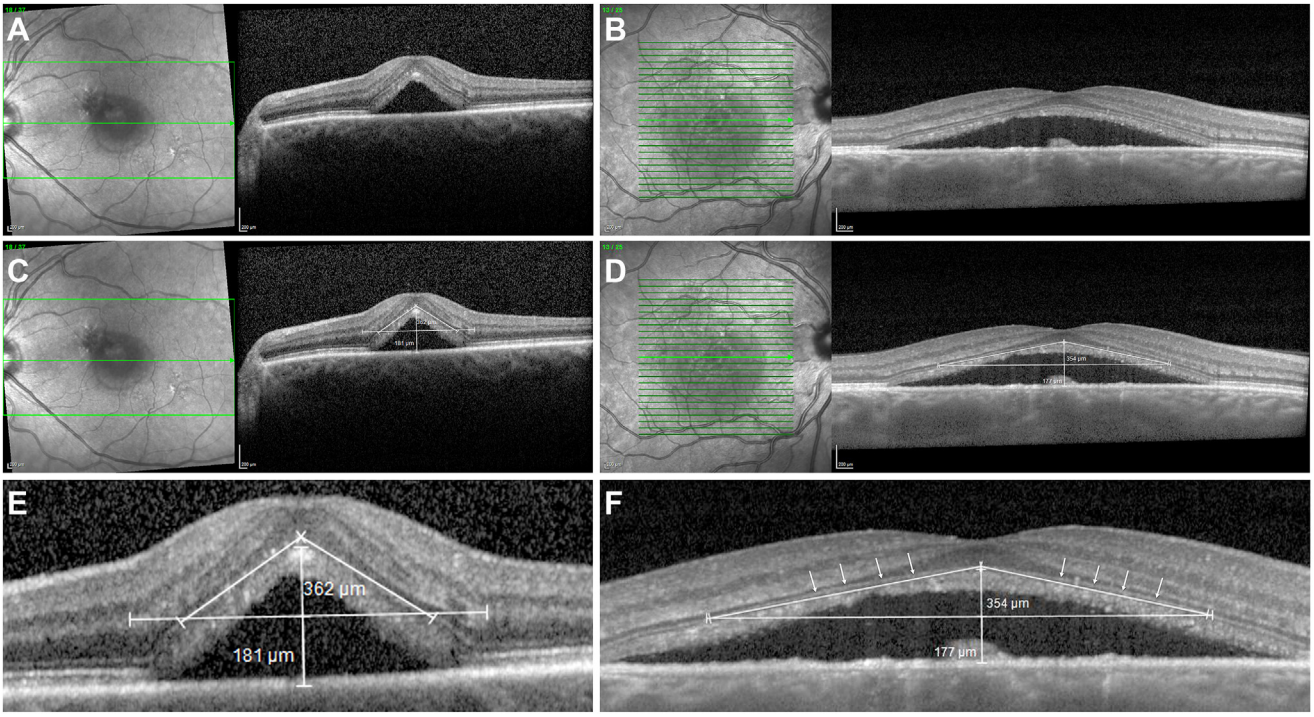

Figure 1. Observed Fuji sign and dome-shaped subretinal fluid (SRF) on OCT scanning of patients with chronic central serous chorioretinopathy (cCSC). **A,** Standard-depth imaging OCT scan of a 60-year-old woman with cCSC in whom the Fuji sign was present at the baseline visit. At 3 months after the baseline visit, the complete resolution of the SRF was observed. This case is an example of when the SRF has steep angles at both ends (as also described in age-related macular degeneration) and; thus, does not meet the Fuji sign criteria, despite the predominantly concave shape of the external limiting membrane (ELM).[7] In view of this, the baseline of the triangle was not located on the Bruch membrane, but instead halfway between the ellipsoid zone and the Bruch membrane to optimally assess the presence of the Fuji sign. **B,** The Fuji sign was confirmed on OCT because the ELM was parallel to the 2 legs of the triangle and did not exceed these lines. **C,** Close-up of the measurement of the Fuji sign. **D,** Enhanced-depth imaging OCT of a 44-year-old man with cCSC, showing dome-shaped SRF at the baseline visit. He had the complete resolution of SRF after receiving half-dose photodynamic therapy during the Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy (PLACE) trial. **E,** The shape of the SRF did not qualify for the Fuji sign because the ELM did protrude on both sides above the 2 legs of the triangle. **F,** Close-up of the measurement of the Fuji sign. The white arrows show the ELM with its concave shape.

examination with OCT should be performed 4 to 8 weeks later.[1,6] If there is still significant SRF at that time point, we recommend that treatment—preferably half-dose photodynamic therapy, if available—should be performed.[1]

Of note, the Fuji sign was also observed in 13.2% of treated control patients, which was expected, as the Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI) trial showed that complete SRF resolution after 12 months occurred in 30% of patients with placebo-treated cCSC.[3] If the focal leakage causing the SRF decreases or disappears, this could mean that the causative choroidal pressure underneath has decreased and the retinal pigment epithelium defect is closing. This would cause the dome-shaped SRF accumulation to collapse into a Mount Fuji-shaped SRF configuration. This is further supported by the fact that the study patients had significantly fewer focal leakage points on FA than the control patients at baseline.

The limitations of this study include its retrospective nature, limited sample size, and follow-up duration. Therefore, additional studies are needed to assess whether our findings can be replicated.

In conclusion, we show that the Fuji sign on OCT and the number of focal leakage points on FA at baseline seem to be important parameters for predicting which treatment-naïve patients with cCSC will experience spontaneous SRF resolution. In these patients, an active monitoring approach may be considered.

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Data collection: Feenstra, Hensman, Gkika, Lipkova, Diederen, Schlingemann, Downes, van Dijk, Boon
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Abbreviations and Acronyms:
cCSC = chronic central serous chorioretinopathy; **CSC** = central serous chorioretinopathy; **FA** = fluorescein angiography; **SRF** = subretinal fluid.

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Outer Retinal Disruption in Early-Onset Birdshot Chorioretinopathy

Birdshot chorioretinopathy (BSCR) is a chronic, bilateral posterior uveitis associated with HLA-A29. Color fundus, fluorescein angiography, and indocyanine green angiography (ICGA) are gold-standard imaging techniques to diagnose and monitor BSCR.[1] Fundus autofluorescence (FAF) and OCT have also provided insights into disease activity and visual prognosis.[1]

Herein, we describe a series of patients with early-onset BSCR and outer retinal disruption (ORD) that resembles acute outer retinopathy seen in other inflammatory retinal diseases.[2,3] This feature is important to recognize as it represents a treatable cause of vision loss. Moreover, because it has not been previously well described in patients with BSCR, it may lead to diagnostic confusion.

This is a multicenter retrospective, longitudinal study of patients evaluated at the uveitis clinics at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois, and the San Raffaele Scientific Institute in Milan, Italy. The study was approved by the institutional review board at both institutions and conformed to the tenets of the Declaration of Helsinki. Informed consent was waived because of the anonymized nature of the data.

Patients with HLA-A29+ BSCR and ORD were included. Outer retinal disruption was identified on OCT as the attenuation of the external limiting membrane or the ellipsoid zone (EZ)/interdigitation zone (IZ). Patients were excluded if they had any other concomitant ocular conditions. All patients underwent workup to exclude autoimmune or infectious etiologies of retinochoroiditis.

Age, sex, past medical history, best-corrected visual acuities (BCVA), and slit-lamp and dilated fundus examination findings were retrieved at presentation and subsequent visits from the electronic records. Multimodal imaging was reviewed by 3 fellowship-trained uveitis specialists (V.M., A.M., M.V.C.) and included color fundus photography, spectral-domain OCT, short-wavelength or green-light FAF, and widefield dye angiography (Spectralis, Heidelberg Engineering or Optos 200Tx). For graphic demonstration, the ICGA of 1 patient was overlapped with binarized en face OCT using Image J (version 1.53). Because of the small numbers, statistical analyses were not pursued.