

ULTRA-WIDEFIELD IMAGING IN THE MANAGEMENT OF UVEITIS

Considerations for supplementing clinical examination of patients with multimodal, multispectral imaging.

BY SUNIL K. SRIVASTAVA, MD



Along with an increasing number of therapeutic options, advances in ocular imaging are accelerating the evolution of retinal medicine. In uveitis management, for example, multimodal, multispectral imaging capabilities have facilitated earlier diagnosis, better treatment decision-making and more efficient monitoring of disease progress and

therapeutic outcomes. This article examines the use of ultra widefield (UWF) retinal imaging and what it may offer for the management of patients with uveitis.

GETTING BETTER INFORMATION

Standard fluorescein angiography (FA) and optical coherence tomography (OCT) have been mainstays in the clinical assessment of uveitis. Recently, UWF retinal imaging, including FA and indocyanine green angiography (ICGA), is becoming an essential component of the assessment of uveitis. (UWF imaging is available on Optos devices, including the most recent California model.) The formal study and increasing use of UWF imaging in this setting is also

improving our understanding of the uveitic disease process and providing enhanced precision in correlating observed pathologic changes with disease activity and prognosis.

A thorough clinical examination remains the foundation of diagnosis in uveitis, but multimodal imaging can provide important supplemental information. Specifically, multimodal imaging offers superior visualization of subtle pathologic changes, which helps improve management of this challenging, highly idiosyncratic condition. Particularly in cases in which the patient has good visual acuity (VA), the evidence of cystoid macular edema (CME) or retinal vascular leakage on multimodal imaging signals active disease and warns us to watch the patient more carefully.

In our clinic, we follow the initial clinical examination with OCT, as it facilitates evaluation of CME and subretinal fluid. FA and ICGA are also critical for assessing choroidal lesions, retinal vasculitis, and vascular perfusion. We have now moved all of our uveitis patients toward UWF FA at the initial visit to ensure that we are not missing important changes in the periphery. As a result, UWF imaging (both color and FA) has become a vital imaging test used in follow-up visits (Figure 1).

Our increased reliance on UWF imaging has been driven by several practical advantages: the convenience of rapid, single-shot, patient-friendly image capture; effective imaging even through small pupils and vitreous haze (VH); multimodal (color, FA, ICG, and autofluorescence) options; and multispectral (532 nm and 635 nm) illumination to highlight different layers of the retina.¹ But perhaps the most important factor influencing the full adoption of UWF imaging in our clinic was the determination that UWF FA provides details difficult to obtain with conventional imaging technology, and that these details improve our diagnoses and enhance our outcomes.

BENEFITS OF GOING WIDE

Although macular pathology has the greatest immediate impact on VA in patients with uveitis, the clinical relevance of findings outside the macula is becoming better appreciated.



AT A GLANCE

- Multimodal imaging offers visualization of subtle pathologic changes, which can help to improve management of patients with uveitis.
- UWF imaging has revealed that much of the pathology associated with uveitis lies in the periphery.
- Ongoing work to automate the detection, quantification, and assessment of pathology will make UWF imaging an even more useful tool.

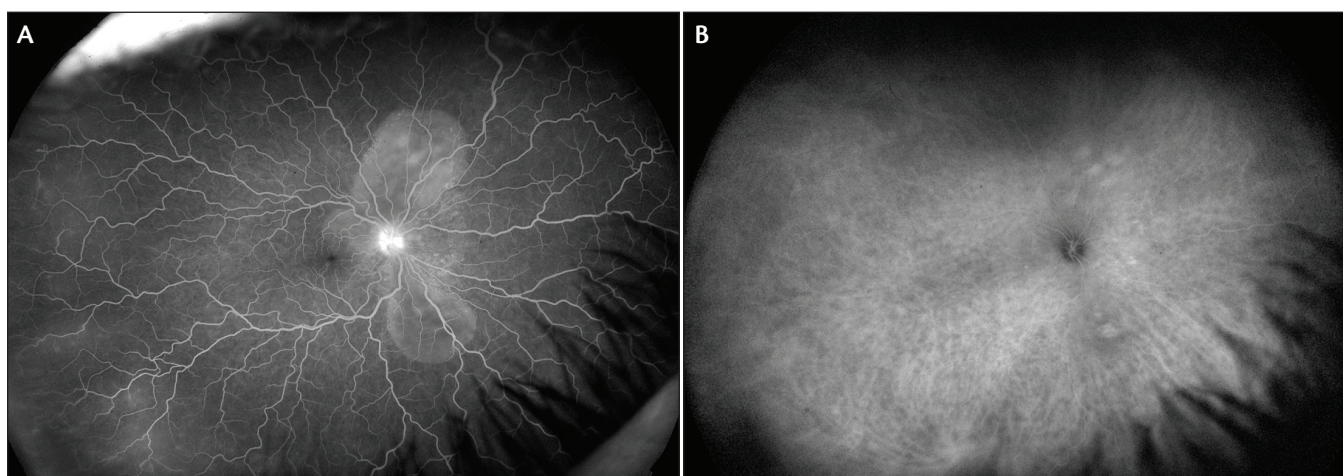


Figure 1. UWF late-frame FA of a patient with panuveitis (A). Note the posterior hyperfluorescence and pooling extending into the midperiphery. The far temporal periphery also reveals retinal vascular wall leakage. The late-frame ICGA (B) highlights diffuse hypofluorescence lesions indicating diffuse choroidal involvement in this patient.

The single-capture, 200° image produced by UWF imaging includes 1.5 times the retinal surface area of a conventional nine-field FA montage.² Thus, with routine UWF imaging we now recognize that much of the pathology associated with uveitis lies in the periphery, and that examination with conventional imaging may miss key signs in this area nearly 30% of the time.

Other investigators have confirmed that UWF FA reveals more pathology in the periphery and posterior pole than conventional imaging. In a study comparing imaging techniques for assessing retinal vasculitis, Leder et al reported that UWF FA revealed more disease activity than standard FA (68% vs. 45%).³ Furthermore, the addition of UWF color and FA imaging altered the management approach in 14% and 51% of visits, respectively.³

The potential effect of incorporating information from UWF imaging into treatment decisions has been explored and confirmed by multiple investigators. In patients with infectious (tuberculosis-associated) posterior uveitis, UWF imaging was used to detect peripheral abnormalities that can help to determine treatment approach, such as the need for immunosuppressive therapy or scatter laser photocoagulation.⁴ Another index study found that management decisions were revised in 48% of patients with noninfectious posterior uveitis with the addition of UWF imaging (combined color and FA), compared with 16% based only on examination and conventional FA. This difference was statistically significant ($P < .001$).⁵

GOING DEEPER

Evidence from UWF imaging may lead us to rethink the treatment approach for individual patients with uveitis, but there is still work to be done to correlate peripheral pathology with the disease process itself and to confirm the clinical

and prognostic significance of these findings. For example, UWF imaging has been shown to be useful in the assessment of VH associated with intermediate, posterior, and panuveitis.⁶ However, as VH is not the only indication for disease activity, ongoing research with UWF imaging may help to determine whether alternative signs of uveitic disease should be given more weight.

Our group recently found that UWF FA revealed more vascular leakage than conventional FA and that this finding was a sensitive surrogate indicator of clinical inflammation, highly correlated with anterior chamber cell and VH.⁷ Vascular leakage may therefore provide an objective measurement to help standardize treatment.⁷ We have also proposed that detection of ischemic peripheral abnormalities (peripheral retinoschisis) in patients with intermediate uveitis and active leakage on UWF FA would suggest the necessity of more active treatment, even in those with good VA.⁸

QUANTITY IS QUALITY

As evidence accumulates regarding the qualitative value of UWF imaging in the understanding and management of uveitis, efforts are also under way to use this high-resolution digital imaging tool to improve the quantification of peripheral retinal pathology in the disease and to confirm the clinical significance of these findings.

Karampelas and colleagues have used UWF FA to quantify vascular abnormalities in a large cohort of patients with the goal of correlating these findings with changes in vision.⁹ They identified relationships between peripheral vessel leakage, vasculitis, and ischemia, but determined that only macular findings (extent of foveal ischemia and increased macular thickness) had an independent association with VA.⁹ However, the association of peripheral focal vasculitis

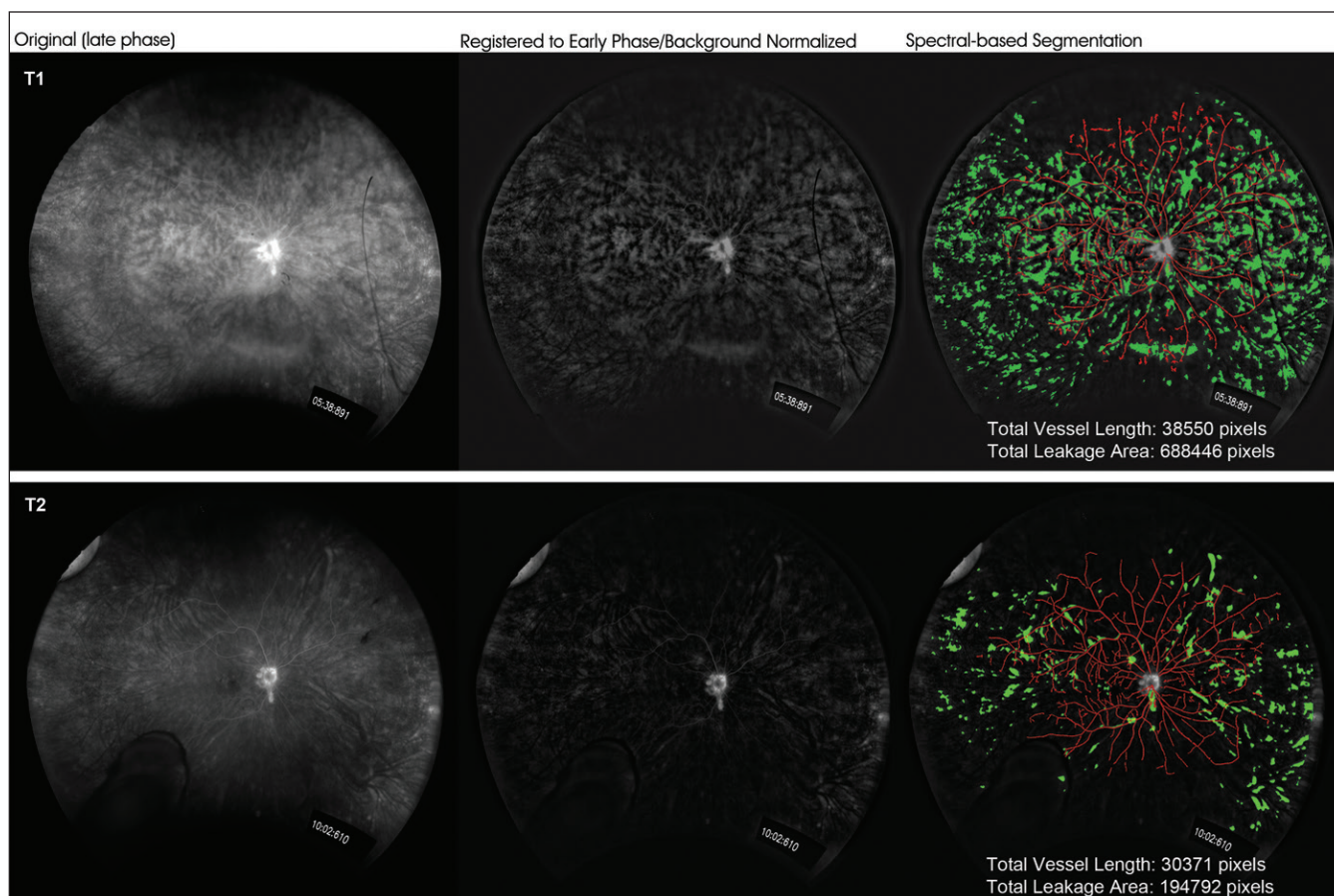


Figure 2. Automated leakage analysis of the same patient prior to treatment with fluocinolone acetone implant (top row) and after treatment (bottom row). First column shows the original image, second column reveals the transformed image after normalizing to the early frame, and right column displays the segmented image. Note the reduction in leakage (in green) between the top and bottom rows.

and diffuse capillary leakage with the development of macular edema and neovascularization suggests that these are important markers of disease activity that could create a rationale for earlier treatment to prevent long-term complications and improve outcomes.

ADVENTURES IN AUTOMATION

Our group has taken the quantification of peripheral pathology with UWF imaging one step further by developing custom image analysis software for the Optos device that automatically and objectively quantifies retinal vascular leakage (Figure 2). To do this, the software transforms the optomap image into a standardized projection that accurately represents the 3-D globe in a 2-D format and then creates a new image that eliminates the retinal vessels and optic nerve to facilitate measurement of only hyperfluorescent perivascular leakage. The final step expresses the total leakage area as a percentage of the total retinal surface area.

To test this new tool, we examined 254 patients with uveitis and identified those with active inflammation. Of 607 eye images deemed to show clinically active inflammation, 100% displayed

vascular leakage. We also performed automated leakage analysis on a subset of 164 images (93 active and 71 inactive) and found a highly significant difference between the mean area of leakage in the two groups (4.4% of total retinal area in eyes with active inflammation vs. 0.9% in eyes with no inflammation; $P < .0001$).¹⁰

By demonstrating a correlation between leakage on UWF FA and active inflammation with an automated detection system, we have identified an objective measure of inflammation that may help guide treatment, facilitate the identification of subclinical inflammation, and provide a more robust clinical endpoint for future clinical trials. Another group has developed and published results using an algorithm on the UWF software platform to automatically detect retinal lesions related to diabetic retinopathy.¹¹ It is hoped that automated detection capabilities such as these will eventually be made commercially available.

ONWARD AND UPWARD

As with other retinal disorders, the more clinically relevant information we have available to help manage patients with uveitis, the better the outcomes we will achieve. Multimodal,

“ Multimodal, multispectral UWF imaging of the entire retina, central pole, and periphery provides an essential and efficient complement to clinical examination and OCT, particularly as the prognostic value of peripheral findings is confirmed.

multispectral UWF imaging of the entire retina, central pole, and periphery provides an essential and efficient complement to clinical examination and OCT, particularly as the prognostic value of peripheral findings is confirmed. Ongoing work to automate the detection, quantification, and assessment of pathology will make UWF imaging an even more useful tool in the future. This research will lay important groundwork for evaluating the efficacy and appropriate role of novel therapies and treatment approaches that emerge over the next few years. ■

1. Knickelbein JE, Hasan J, Nussenblatt RB, Sen HN. Delineation of choroidal and retinal lesions in posterior uveitis by multispectral wide-field scanner laser ophthalmoscopy. *Retina*. 2016;36(11):2213-2219.
2. Nicholson BP, Nigam D, Miller D, et al. Comparison of wide-field fluorescein angiography and nine-field montage angiography in uveitis. *Am J Ophthalmol*. 2014;157(3):673-677.
3. Leder HA, Campbell JP, Sepah YJ, et al. Ultra-wide-field retinal imaging in the management of non-infectious retinal vasculitis. *J Ophthalmic Inflamm Infect*. 2013;3(1):30.
4. Aggarwal K, Mukutkar S, Mahajan S, et al. Role of ultra-wide field imaging in the management of tubercular posterior uveitis. *Ocul Immunol Inflamm*. 2016;24(6):631-636.
5. Campbell JP, Leder AH, Sepah YJ, et al. Wide-field retinal imaging in the management of noninfectious posterior uveitis. *Am J Ophthalmol*. 2012;154(5):908-911.e2.
6. Dickson D, Agarwal A, Sadiq MA, et al. Assessment of vitreous haze using ultra-wide field retinal imaging. *J Ophthalmic Inflamm Infect*. 2016;6(1):35.
7. Pecen PE, Petro KF, Baynes K, et al. Peripheral findings and retinal vascular leakage on ultra-widefield fluorescein angiography in patients with uveitis. *Ophthalmology Retina*. 2017;1(5):428-434.
8. Pichi F, Srivastava SK, Nucci P, Baynes K, Neri, Lowder CY. Peripheral retinosis in intermediate uveitis [published online ahead of print January 11, 2017]. *Retina*.
9. Karampelas M, Sim DA, Chu C, et al. Quantitative analysis of peripheral vasculitis, ischemia, and vascular leakage in uveitis using ultra-widefield fluorescein angiography. *Am J Ophthalmol*. 2015; 159(6):1161-1168.
10. Pecen P, Farhang K, Baynes K. Automated measure of retinal vascular leakage on ultra-widefield fluorescein angiography in patients with uveitis. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2015; Denver, CO.
11. Wang K, Jayadev C, Nittala MG, et al. Automated detection of diabetic retinopathy lesions on ultrawidefield pseudocolor images [published online ahead of print September 19, 2017]. *Acta Ophthalmologica*.

Sunil K. Srivastava, MD

- staff physician at Cole Eye Institute, Cleveland Clinic, Ohio
- financial disclosure: consultant/advisory board for Optos, Zeiss
- srivass2@ccf.org