In Vivo Confocal Microscopy of Keratic Precipitates

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Objective: To evaluate the heterogeneity of keratic precipitates (KP) in varying subtypes of uveitis by in vivo confocal microscopy (IVCM).

Methods: The KP were viewed with a scanning confocal microscope in patients (n=33) who sought care at a tertiary referral uveitis service for immune-mediated and infectious forms of uveitis, including HLA-B27–associated uveitis, sarcoidosis, Vogt-Koyanagi-Harada syndrome, juvenile chronic arthritis, Fuchs heterochromic iridocyclitis, cytomegalovirus retinitis, herpes zoster ophthalmicus, ocular toxoplasmosis, and idiopathic uveitis. Images were captured and digitalized in real time.

Results: Forty-two eyes of 33 patients were examined in this study. Patient age ranged from 22 to 84 years, with a mean age of 49.4 years. Seventeen (52%) of the patients were women, and 16 patients (48%) were men. The KP ranged in diameter from 10 to 350 µm. We observed the following absolute and speculative outcomes: KP are markedly heterogeneous and variable as documented by IVCM; KP in individual patients are consistent throughout the cornea; the morphologic features of KP change across time; infectious vs noninfectious causes of uveitis seem to be readily distinguishable by using IVCM; and KP may have consistency for specific disease states and therefore may have diagnostic importance.

Conclusions: To our knowledge, this is the first time that IVCM has been used to describe the architecture and heterogeneity of KP in uveitis. Such observations reveal a heterogeneity that could not be appreciated by conventional slitlamp microscopy and may have diagnostic relevance.

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FORMATION OF KERATIC PRECIPITATES (KP) is a characteristic finding in various forms of intraocular inflammation, including uveitis and corneal transplant rejection. Generally, KP are created by the clustering of cells with adherence to the corneal endothelium. Typically, these clusters are composed of epithelioid cells, lymphocytes, and polymorphonuclear cells.1 Generally, KP are classified into 2 major subgroups: granulomatous and nongranulomatous. Specific nomenclature has isolated certain subtypes of KP as in the stellate KP seen in Fuchs heterochromic iridocyclitis. Limited information exists on the histologic characteristics of KP. To our knowledge, no studies have examined the specific histopathologic features of KP in different disease states. One study2 used specular microscopy to describe the morphologic features of endothelial deposits in patients with cytomegalovirus retinitis. The reason for this paucity in the literature is simply that samples of KP in specific active diseases are impossible to obtain without destroying the corneal endothelium, performing a penetrating keratoplasty, or waiting for postmortem examination. Therefore, KP have been seen as an interesting by-product of inflammation and have played, until now, a limited role in the actual diagnosis and management of intraocular inflammation.

As its name reveals, the confocal microscope’s success revolves around the fact that both the observation and illumination systems can be focused on a single (confocal) point.3 This allows for excellent lateral (x-axis, y-axis) and axial (z-axis) resolution. Because the confocal microscope relies on a single point of reference, the field of view is grossly limited. This is overcome by the rapid-scanning component of the microscope, which uses a spinning metal plate that consists of a series of microscopic holes called a Nipkow disk, thus enabling reconstruction of the image with real-time viewing on-screen.4 Confocal microscopy allows in vivo examination of the human cornea at all cellular levels. Physicians have used the confocal microscope to view the different layers of the corneal epithelium, Bowman membrane, stromal constituents (including kerato-
cytes and corneal nerves), Descemet membrane, and endothelium. No study, to our knowledge, has ever specifically examined KP on the corneal endothelium using this system.

This study evaluates the heterogeneity of KP in varying subtypes of uveitis by in vivo confocal microscopy (IVCM). We propose that with the use of IVCM of KP, the physician can make intelligent suppositions that may help with the diagnosis and subsequent treatment of the patient with intraocular inflammation. This method of confocal microscopy permits the evaluation of KP with enhanced detail so that a differential diagnosis might be possible based on what adheres to the corneal endothelium and what lies beyond.

**METHODS**

**PATIENTS**

This study was approved by Oregon Health & Science University’s institutional review board. Patients 18 years or older who attended either the tertiary referral Inflammatory Eye Disease Clinic or the Adult Eye Clinic at the Casey Eye Institute and who had evidence of KP from previous or active ocular inflammation were invited to participate in a study to delineate the morphologic features and extent of their KP using IVCM. Each patient signed an informed consent form before participation. Data collection included age, sex, ethnicity, ocular diagnosis and duration thereof, disease activity, current topical and systemic medication, and slitlamp color photographs or detailed documentation and description of the KP.

The ocular diagnoses were made using standard departmental protocols. This included a thorough history, including extensive review of systems, ophthalmic examination, and pertinent laboratory or radiologic investigations. The general approach of this institution to differential diagnosis has been previously described. Some examples include the following. Ocular toxoplasmosis was diagnosed with the combination of a typical clinical picture of a chorioretinal scar and positive titers of immunoglobulins. Cytomegalovirus retinitis was diagnosed based on clinical appearance in an immunocompromised host and response to appropriate therapy. We diagnosed HLA-B27–associated uveitis in patients with acute-onset, unilateral, anterior uveitis who had a positive test result for the HLA-B27 antigen with or without associated back symptoms. Vogt-Koyanagi-Harada syndrome was diagnosed according to international consensus group recommendations.

**IN VIVO CONFOCAL MICROSCOPY**

Patients’ corneas and KP were viewed with a scanning confocal microscope (ASL-1000; Advanced Scanning Ltd, New...
Forty-two eyes of 33 patients were examined in this study. The ages of patients ranged from 22 to 84 years, with a mean age of 49.4 years. Seventeen (52%) of the patients were women, and 16 (48%) patients were men. All but 5 patients were white and had varying diagnoses (Table). The KP varied in diameter from 10 to 350 µm. Because this is a unique study that describes high-powered images of KP, we propose our own illustrative and morphologic terms and use them descriptively in the table and figures that follow. After reviewing all of the images, we decided on 6 umbrella terms to describe the KP: globular, infiltrating, smooth-rounded, stippled, dendritiform, and cruciform.

Keratic precipitates are far more heterogeneous and variable on IVCM compared with standard, low-powered slitlamp biomicroscopy (SLB) (Figure 1). Figure 1 shows images of an 84-year-old man who was diagnosed as having postoperative endophthalmitis. The detail of the architecture and heterogeneity of KP are far more discernible using IVCM compared with standard SLB. The standard SLB photograph of the cornea and anterior segment (Figure 1A) reveals diffuse granulomatous KP scattered throughout the endothelium. In vivo confocal microscopy reveals large, infiltrating KP (Figure 1B) that correspond to the large opacities on the SLB photograph (A). It is evident that large KP are made up of individual cellular components clustered together. Note the soft, infiltrating border to the KP; this was a frequent finding in patients with infectious causes of uveitis. Between the large KP, IVCM reveals patches of fibrinlike material and cellular compo-

Figure 1. Standard keratic precipitates (KP) are far more heterogeneous and variable on in vivo confocal microscopy (IVCM) than with standard, low-powered slitlamp biomicroscopy (SLB). A, Standard SLB photograph of the cornea and anterior segment, revealing diffuse granulomatous KP scattered throughout the endothelium. B, The IVCM photograph reveals large, infiltrating KP that correspond to the large opacities on the SLB photograph (A). C, The IVCM was performed on an area of the endothelium between the large granulomatous KP. This area shows fibrinlike material adherent to the endothelium. ASL indicates Advanced Scanning Ltd (New Orleans, La). The depth from corneal epithelium at which the image was captured is indicated in micrometers.
nosed as having bilateral granulomatous uveitis secondary to sarcoidosis. She had 2+ cellular activity in her anterior chamber at the time of IVCM and was not receiving topical or systemic therapy. The central cornea was imaged using IVCM and revealed multiple globular KP (Figure 2A). The peripheral cornea showed consistent globular KP in the same individual (Figure 2B). We performed IVCM in a 59-year-old white woman who had the diagnosis of idiopathic granulomatous uveitis (Figure 2C and D). Disease activity at the time of IVCM was 2+ anterior chamber cells, and she was taking 1% prednisone acetate hourly for the affected eye. The IVCM of her peripheral cornea revealed a globular, stippled pattern of KP (Figure 2C). A slightly more central view of the KP showed consistent morphologic features (Figure 2D). The IVCM was performed in a 31-year-old Asian man who also had the diagnosis of idiopathic granulomatous uveitis (Figure 2E and F). He had mild disease activity at the time of IVCM, with only trace cells in the anterior chamber, and was taking 1% prednisone acetate 3 times per week for the affected eye. The central cornea shows smooth-rounded KP (Figure 2E), and the peripheral cornea shows a similar, consistent smooth-rounded KP (Figure 2F).

The morphologic features of KP change across time, including a change with disease progression and treatment (Figure 3). Figure 3 shows IVCM images taken during a 3-week time frame of a 53-year-old white man with the diagnosis of idiopathic unilateral panuveitis. He received follow-up in the clinic for a 3-week period. At initial ex-
amination and before topical treatment, the KP showed a stippled pattern and were consistent throughout the affected cornea (Figure 3A). He began using topical 1% prednisolone acetate hourly and was evaluated 5 days later. At 5 days after the initiation of therapy, his stippled pattern had changed to a smooth-rounded pattern (Figure 3B), and this too was consistent throughout the affected cornea. Twelve days after he initiated steroid therapy, his uveitis showed only mild activity, and his KP had nearly disappeared. Only small, pigmented KP were observed on SLB. Pigment tends to shine brightly on IVCM (Figure 3C). The shape and morphologic features of KP tend to change across time. Not only have these changes been seen in treated patients (Figure 3), we have also noted them in disease progression with IVCM.

Infectious vs noninfectious causes of uveitis seem to be readily distinguishable by using IVCM (Figure 4 and Figure 5). Infectious causes of KP seem to have an infiltrating and dendritic appearance (Figure 4). Walter et al performed a postmortem examination in a patient with cytomegalovirus retinitis and observed chains of dendritic macrophages and fibrin adherent to the apical surface of the corneal endothelium. We observed similar appearances in our patients with infectious disease etiologies. Noninfectious causes appear to result in KP that tend to be more smooth-rounded and globular (Figure 5). The IVCM was performed in a 62-year-old white man with a diagnosis of unilateral ocular toxoplasmosis. He had positive IgM and IgG antibodies with a typical chorioretinal scar (Figure 4A and B). Figure 4A shows infiltrating KP with globular central cores and dendritic pseudopodia, which we typically see in infectious causes of uveitis. Figure 4B reveals an area of the cornea between the larger KP, showing multiple dendritic bodies. The IVCM was performed in a 71-year-old white man with stage III multiple myeloma undergoing chemotherapy. He had a classic diagnosis and appearance of cytomegalovirus retinitis with a positive serum test result for antibodies (Figure 4C and D). Disease activity at the time of IVCM showed 1+ anterior chamber cells with flare. The IVCM revealed a similar infiltrating appearance to that seen in the toxoplasmosis case with dendritic pseudopodia (Figure 4C). The image shown in Figure 4C was taken at the endothelial layer; the image shown in Figure 4D was taken at a slightly deeper level to the endothelium. We performed IVCM on a 59-year-old white woman with the diagnosis of herpes zoster ophthalmicus (Figure 4E). The typical infectious signs are seen yet again in this example: central globular KP with infiltrating dendritic pseudopodia. There is a striking similarity among all the images in Figure 4, and there is an obvious difference when comparing them with the KP in the noninfectious causes of uveitis (Figure 5).

Noninfectious granulomatous conditions are illustrated in Figure 5. At initial glance, the differences between the images in Figure 4 (infectious causes) and Figure 5 are striking and obvious. The infiltrating or dendritic appearance gives way to globular and smooth-rounded KP. The IVCM was performed in a 32-year-old white woman with the diagnosis of Vogt-Koyanagi-Harada syndrome with serous retinal detachments (Figure 5A). Her inflammation was not active at the time of IVCM. The image reveals globular KP without an infiltrating appearance. The globular appearance of the KP is emphasized in a 3-dimensional reconstruction of the KP (Figure 5B). This 3-dimensional image was rendered from z-stacks taken with the confocal microscope. The IVCM was performed in a 60-year-old white woman who also had a diagnosis of Vogt-Koyanagi-Harada syndrome with serous retinal detachments (Figure 5C). The image was taken while there was significant inflammation, with 3+ anterior chamber and 2+ vitreous activity. The IVCM shows globular, noninfiltrating KP. We performed IVCM in a 31-year-old Asian man with the diagnosis of idiopathic granulomatous uveitis (Figure 5D). This oblique image reveals smooth-
rounded KP at the level of the endothelium. He had mild disease activity at the time with only trace cells in the anterior chamber. Figure 5E represents an image of KP in a 35-year-old African American woman with the diagnosis of bilateral granulomatous uveitis secondary to sarcoidosis. A separate image from this patient is seen in Figure 2A and B. The KP imaged are multiple with a globular appearance. This patient had 2+ cellular activity at the time of IVCM. The final image, Figure 5F, is an IVCM image of a 45-year-old white man with the diagnosis of biopsy-proven sarcoidosis. He had mild disease activity at the time of imaging. The imaged KP have a globular appearance.

The KP may have consistency for specific disease states and therefore may have diagnostic importance (Figure 6). We used IVCM to image the KP of 6 patients with active HLA-B27–associated uveitis (Figure 6A-E). The prominent feature noted was that all of the KP had a stippled appearance and that they had no obvious similarity to the other KP imaged. These KP seem to be made up of individual cells, as seen most clearly in Figure 6A and B. Lymphocytes measure between 8 and 12 µm, and polymorphs measure approximately 10 to 12 µm in diameter. These sizes correspond to the stippled areas seen in Figures 6A-E. We therefore believe that the KP in HLA-B27–associated uveitis are made up of mainly single but at times small clusters of individual leukocytes. For 1 of the 6 patients with HLA-B27–associated uveitis, the images were of poor quality and are therefore not reproduced.
COMMENT

In vivo confocal microscopy has been effectively applied to diagnosing and describing corneal disease. Numerous case reports and studies9-26 have used IVCM to concentrate on keratitis, keratopathies, and other inflammatory diseases of the cornea and endothelium. However, to our knowledge, there has never been a case report or study that concentrates solely on the appearance of KP by IVCM in different disease states.

Specular microscopy has been used to image the corneal endothelium in various diseases.2,27 One study examined KP by using specular microscopy and focused largely on the appearance and consequence of the surrounding endothelium in 13 patients with differing diagnoses.27

Although this is an initial study of KP, several novel conclusions are apparent. First, not surprisingly, KP show far greater heterogeneity using IVCM compared with SLB. Despite their heterogeneity, morphologic features in individual patients and their fellow eyes are consistent. Certainly, this suggests that the adhesion molecules and inflammatory mediators are consistent for different locations in the cornea in a single patient. Second, our longitudinal experience with patients is that the morphologic features of KP change with time. Accordingly, in diseases such as Fuchs heterochromic iridocyclitis, we have observed diversity in morphologic features, which we believe reflects disease duration and treatment rather than heterogeneity in origin. Further experience will adequately test this speculation.

Figure 5. In vivo confocal microscopy (IVCM) of keratic precipitates (KP) in noninfectious causes of uveitis. A, The IVCM photograph of KP in a patient with Vogt-Koyanagi-Harada syndrome. The image reveals globular KP without an infiltrating appearance. B, The globular appearance of these KP is emphasized by a 3-dimensional reconstruction of the KP. C, The IVCM photograph of another patient with Vogt-Koyanagi-Harada syndrome, showing globular, noninfiltrating KP. D, The IVCM photograph of KP in a patient with idiopathic granulomatous uveitis. The oblique image reveals smooth-rounded KP at the level of the endothelium. E, The IVCM photograph of KP in a patient with sarcoidosis uveitis, showing multiple KP with a globular appearance. F, The IVCM photograph of another patient with sarcoidosis, showing KP with a globular appearance. ASL indicates Advanced Scanning Ltd (New Orleans, La). The depth from corneal epithelium at which the image was captured is indicated in micrometers.
Preliminary experience in observing patients with infectious causes of uveitis has shown that in all 9 patients with active infection of diverse etiology, the morphologic features of KP are distinctive with an infiltrating or dendritiform appearance. In our practice, we commonly encounter patients for whom an infectious cause of uveitis is suspected but not proved. Clearly, treatment is influenced by this distinction. Only much greater experience with IVCM will allow us to determine if the appearance of KP secondary to infection is sufficiently consistent such that therapeutic decisions can be based on the image.

The HLA-B27–associated uveitis was the disease that we had the most opportunity to evaluate. We have observed great consistency in these KP. This observation leads us to speculate that IVCM may become an important tool in differential diagnosis. However, we have not had the opportunity to image acute-onset, nongranulomatous iritis in a patient who has a negative test result for the HLA-B27 antigen. Additional study will be required to determine the specificity of the stippled, unicellular appearance of KP that we see in patients who have a positive test result for this antigen.

To date, KP have received scant scrutiny. This study makes clear that a wealth of information could be gained by categorizing and defining their detailed structure. Morphometric analysis and correlative histologic and immunohistochemical analysis of individual KP in certain disease states may give further clues to the specific composition and pathogenesis of KP. With this basic information and a database of KP images in different diseases, noninvasive IVCM may become an adjunctive investigational and diagnostic tool. The relatively small number of patients in each clinical category in this study indicates that further studies are required to more clearly define the KP in each condition.

Figure 6. In vivo confocal microscopy images of keratic precipitates (KP) of 5 patients with active HLA-B27–associated uveitis. All of the KP had a stippled appearance. ASL indicates Advanced Scanning Ltd (New Orleans, La). The depth from corneal epithelium at which the images were captured is indicated in micrometers.
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