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LABORATORY STUDY

Keratic precipitate morphology in uveitic syndromes including Behçet's disease as evaluated with *in vivo* confocal microscopy

MC Mocan, S Kadayifcilar and M Irkec

Abstract

Purpose **To identify the morphologic appearance of keratic precipitates (KPs) with *in vivo* confocal microscopy (IVCM) in uveitic syndromes.**

Methods **A total of 75 eyes of 72 patients with a mean age of 38.6 ± 15.1 years who had active intraocular inflammation and whose corneas had KP on slit-lamp examination were included in this study. IVCM (Confoscan 3.0, Vigonza, Italy) was used to image the part of the corneal endothelium in which KP were most densely deposited. KP were classified into five groups: type I (small, round), type II (stippled), type III (dendritiform), type IV (large, smooth-rounded), and type V (globular). When more than one type of KP was observed with IVCM, a distinction between the predominant and the less frequent KP was made as 'primary' and 'secondary' KP.**

Results **In 50 (66.7%) eyes more than one type of KP was imaged. The size of the KP ranged between 5 and 150 μm. The most frequently observed primary KP type in Behçet's disease was type I (100%), in ankylosing spondylitis type II (57.1%), in Fuchs' uveitis syndrome type III (85.7%), in granulomatous uveitis type V (42.9%), in infectious uveitis type III (66.7%), and in juvenile idiopathic arthritis associated uveitis type I (66.7%). The KP types showed a statistically significant difference between different uveitic syndromes (Fisher's exact test, $P<0.001$).**

Conclusions **Certain KP types appear to be characteristic of various uveitic syndromes. IVCM may have a potential role in the diagnostic work-up of uveitic patients.**

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Introduction

Keratic precipitates (KPs) are corneal endothelial deposits that are frequently observed in association with anterior segment inflammation.[1] These precipitates are formed by the aggregation of polymorphonuclear cells, lymphocytes, and epitheloid cells.[1,2] In the setting of uveitis, the biomicroscopic appearance of KP may yield important diagnostic clues for the identification of the underlying inflammatory disorder.[1] Typically, small, round, and whitish precipitates are observed in non-granulomatous uveitis whereas large, yellowish (mutton-fat) KP are more characteristic of granulomatous inflammation.[1] Moreover, stellate KP are frequently associated with Fuchs' uveitis syndrome[3] and pigmented vertical linear precipitates are suggestive of pigment dispersion syndrome.[4] However, a more detailed examination of KP morphology is not possible due to the limited magnification of slit-lamp examination (SLE).

In vivo confocal microscopy (IVCM) has enabled the high resolution (1 μm) and magnified (× 500) imaging of the living cornea and is being increasingly used to evaluate corneal disorders such as keratoconus, infective keratitis, corneal dystrophies, diabetic keratopathy, postrefractive surgery corneas, and in the setting of contact lens use.[5] However, the evaluation of KP with IVCM has been limited;

Department of Ophthalmology, Hacettepe University School of Medicine, Ankara, Turkey

Correspondence: M Irkec, Department of Ophthalmology, Hacettepe Üniversitesi, Göz Hastalýklarý Anabilim Dalý, Sýhhiye, Ankara 06100, Turkey
Tel: +90 312 3051777; Fax: +90 312 3094101.
E-mail: mirkec@isnet.net.tr

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the literature contains one report by Wertheim *et al*[2] in 2004 of findings in 33 patients with different forms of uveitis.

The purpose of this study was to identify the morphologic appearance of KP with IVCM in several common uveitic syndromes including Behçet's disease and to determine whether certain KP types were more frequently associated with specific uveitis syndromes.

Materials and methods

Participants

The study was undertaken at a single university based hospital. Patients who were evaluated with the diagnosis of uveitis, who had active intraocular inflammation at the time of evaluation, and whose corneas had evidence of KP on slit-lamp biomicroscopic examination were included in this study. All patients were evaluated by a uveitis expert (SK) who had significant experience in the diagnosis and management of intraocular inflammation.

The diagnosis of uveitis and specific uveitis syndromes were made by a combination of clinical evaluation and laboratory testing where necessary. Behçet's disease was diagnosed when the combination of recurrent uveitis, recurrent oral ulcers, genital ulcers with or without skin lesions/positive pathergy test were present. Only established Behçet's cases fulfilling major criteria put forward by the International Study Group for Behçet's Disease[6] were included in the study. The diagnosis of Fuchs' uveitis syndrome was made when a unilateral chronic low-grade inflammation ($\leqslant +2$ cells in the anterior chamber) was accompanied by iris atrophy and absence of posterior synechiae with or without heterochromia in an adult patient.[3] The diagnostic criteria for ankylosing spondylitis included the documented presence of recurrent anterior uveitis together with chronic low back stiffness of at least 3 months' duration, radiologic evidence of sacroiliitis on magnetic resonance imaging and HLA-B27 positivity.[7] Granulomatous uveitis was diagnosed in the setting of chronic intraocular inflammation, large mutton-fat KPs with or without the presence of iris or pupillary nodules. Ocular toxoplasmosis was diagnosed in the presence of a characteristic chorioretinal scar and positive immunoglobulin titers. Cytomegalovirus retinitis was diagnosed based on the presence of typical peripheral retinitis in an immunocompromised patient. Herpetic uveitis was diagnosed in the setting of uveitis and suggestive corneal involvement. Juvenile idiopathic arthritis (JIA)-associated uveitis was diagnosed in paediatric patients who presented anterior uveitis with or without the presence of vitreous cells, minimal ciliary injection, and who were under the care of the paediatric rheumatology department with an established diagnosis of JIA. Patients in whom uveitis was not found to be associated with any underlying ocular or systemic condition at the time of the most recent evaluation were classified under idiopathic uveitis. The extent of ocular involvement was evaluated and classified as anterior, intermediate, posterior or panuveitis. Clinically, KPs were classified in three subgroups based on their size (fine, medium, large) as observed through biomicroscopy. Fine KPs were defined as very small, dust-like round precipitates that could be discerned with high magnification of the biomicroscope. Large KP were defined as coarse, round and creamy-white yellowish precipitates that could be easily visualized with lower magnification of the biomicroscope, appeared opaque, and were usually localized to the inferior corneal endothelium. Medium KPs were defined as precipitates whose sizes were in between those of fine and large KPs. The corneal endothelium of all patients were examined and imaged with IVCM during active uveitis before initiation of appropriate treatment.

Informed consent was obtained from all patients and the study was carried out with approval from the Institutional Review Board.

Confocal microscopy in vivo

IVCM was performed by a single observer (MCM) who had experience in this technique using Confoscan 3.0 (Vigonza, Italy) attached to an immersion lens (Achroplan $\times 40/0.75$W; Zeiss, Germany). The immersion lens had a working distance of 1.98 mm, a numerical aperture of 0.75 and a front area of 16.61 mm. The technique is described in detail elsewhere.[8] Before image acquisition, the corneal endothelium was examined with SLE to identify the region of the cornea in which the KPs were most densely deposited. This area was determined to be either the central or the inferior paracentral cornea for all cases studied. IVCM was specifically performed on this region. For each patient, four to six corneal scans of the posterior cornea including the endothelium and the posterior stroma were obtained. Total duration of the confocal microscopic examination lasted for about 2 min and image acquisition time lasted for approximately 60 s. The images represented an area of $450 \times 340\,\mu$m, had a lateral resolution of $1\,\mu$m, and a depth (z axis) resolution of $10\,\mu$m. The mean magnification obtained was $\times 500$ on a 15″ display (1024×768 pixels).

Image analysis

KPs were evaluated in the best-focused images for endothelial layer that had sufficient clarity and detail by

a single observer (MI) who was masked to the patients' eye disease status. Based on previous and current observations of KPs with IVCM in our clinic, the corneal deposits were classified in five groups similar to the grading system described by Wertheim *et al*[2] as follows: type I (small, round), type II (stippled), type III (dendritiform), type IV (large, smooth-rounded), and type V (globular; large and harbouring multiple hyper-reflective round inclusions in a conglomerate appearance; Figure 1a–e). When more than one type of KP was observed with IVCM, a distinction between the predominant and the less frequent KP was made as 'primary' and 'secondary' KP.

Statistical analysis

Statistical analyses were performed using SPSS version 12.5 (Chicago, IL, USA) software. Fisher's exact test was used to determine whether KP types were different between different uveitic syndromes. A *P*-value of less than 0.05 was considered significant.

Results

A total of 75 eyes of 72 patients (28 women, 44 men) with a mean age of 38.6 ± 15.1 years (range = 11–81 years) were included in the study. The number of eyes included in each uveitic syndrome is presented in Table 1. Fifty-five (73.3%) eyes had anterior uveitis, one (1.3%) eye had intermediate uveitis, five (6.7%) patients had posterior uveitis, and fourteen (18.7%) had panuveitis (Table 1). Nine (12%) eyes had evidence of granulomatous uveitis. Of the seven patients with granulomatous uveitis, four had clinical and laboratory findings consistent with sarcoidosis. Of the six cases with infectious uveitis, two had ocular toxoplasmosis, three had herpetic uveitis (two with herpes zoster virus and one with herpes simplex virus) and one had cytomegalovirus related posterior uveitis. The underlying cause for uveitis was undetermined (ie, idiopathic) in 13 patients (17.3%) at their most recent evaluation. Slit-lamp biomicroscopy revealed fine KP in 46 (61.3%) eyes, medium-sized KP in 20 (26.7%) eyes, and large KP in 9 (12%) eyes.

In 50 (66.7%) eyes more than one type of KP was imaged (Table 2). The size of the KP ranged between 5 and 150 μm. More specifically, the size range of type I KP was 5–10 μm, type II was 5–15 μm, type III was 30–100 μm, type IV was 40–150 μm, and type V was 50–100 μm.

Of the 46 eyes that had fine corneal deposits as seen with SLE, the most frequently imaged primary KP as imaged with IVCM were type I in 26 (56.5%) and type II in 11 (23.9%) eyes (Figure 1). Of the 20 corneas with

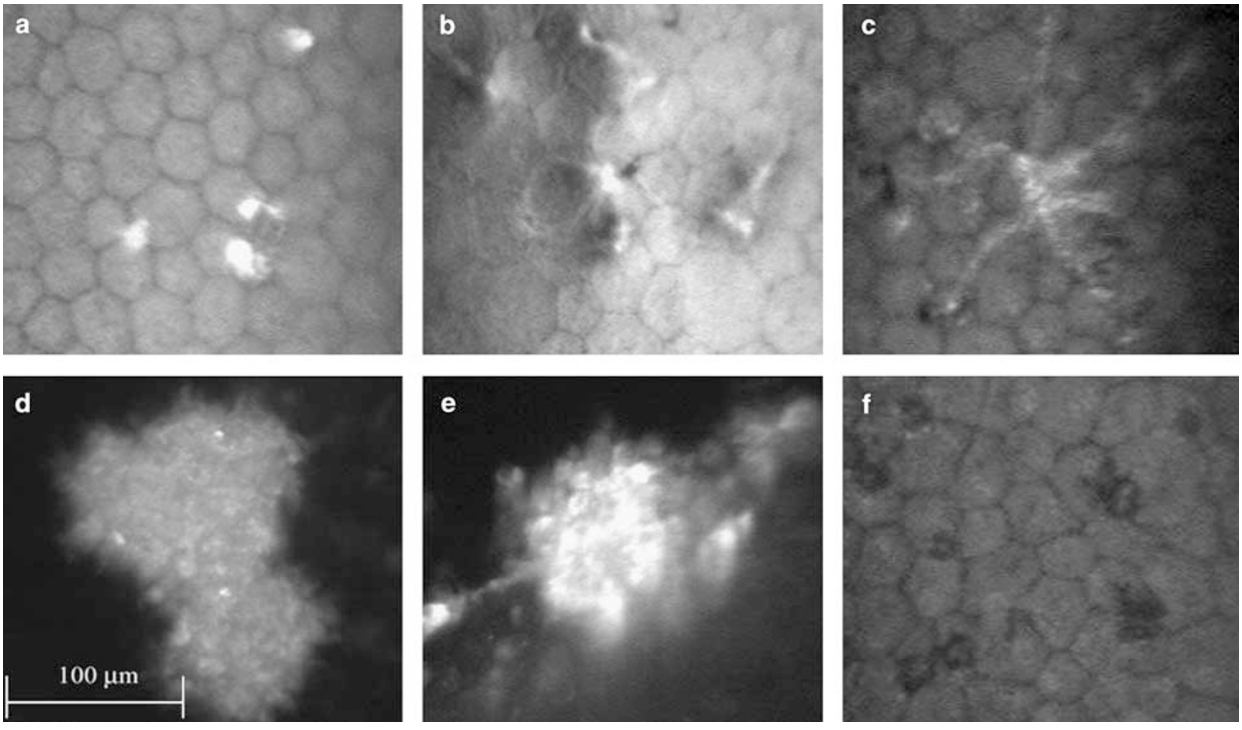

Figure 1 The appearances of keratic precipitate (KP) morphology with *in vivo* confocal microscopy. (a) Small and round KP (centre of image). (b) Stippled KP. (c) Dendritiform KP with threadlike extensions across the endothelium. (d) Large and smooth-rounded KP. (e) Globular KP, large and harbouring multiple hyper-reflective round inclusions in a conglomerate appearance. (f) Endothelial blebs observed as empty lacunae.

Table 1 The clinical characteristics of uveitis in the study group

Aetiology	*Extent of intraocular inflammation*			
	Anterior (%)	*Intermediate (%)*	*Posterior (%)*	*Panuveitis (%)*
Behçet's disease ($n=18$)	7 (38.9)	—	—	11 (60.1)
Ankylosing spondylitis ($n=14$)	14 (100)	—	—	—
Fuchs' uveitis syndrome ($n=14$)	14 (100)	—	—	—
Granulomatous ($n=7$)	4 (57.1)	—	—	3 (42.9)
Infectious ($n=6$)	3 (42.9)	—	4 (57.1)	—
Juvenile idiopathic arthritis ($n=3$)	3 (100)	—	—	—
Idiopathic ($n=13$)	11 (84.6)	1 (7.7)	1 (7.7)	—

Table 2 The morphology of keratic precipitates as observed through *in vivo* confocal microscopy in various uveitic disorders

Aetiology	*Morphology of keratic precipitates*					*Total*	
	I Small round	*II Stipppled*	*III Dendritiform*	*IV Large smooth*	*V Globular*		
Behçet's disease (n = *18)*							
1°	18	—	—	—	—	18	24
2°	—	5	1	—	—	6	
Ankylosing spondylitis (n = *14)*							
1°	2	8	3	—	1	14	25
2°	3	5	3	—	—	11	
Fuchs' uveitis syndrome (n = *14)*							
1°	—	2	12	—	—	14	26
2°	—	3	2	4	3	12	
Granulomatous (n = *7)*							
1°	—	2	—	2	3	7	13
2°	—	2	3	1	—	6	
Infectious (n = *6)*							
1°	2	—	4	—	—	6	9
2°	—	1	—	—	2	3	
Juvenile idiopathic arthritis (n = *3)*							
1°	2	1	—	—	—	3	5
2°	1	1	—	—	—	2	
Idiopathic (n = *13)*							
1°	4	3	5	1	—	13	23
2°	3	5	1	—	1	10	

medium-sized corneal deposits, the most frequent primary KP was type III in 14 (70%) eyes. Finally, of the nine eyes with large corneal deposits, the most frequent primary KP observed were type IV in three (33.3%) eyes and type V in three (33.3%) eyes (Figure 2).

The most frequently observed primary KP type in Behçet's disease was type I (100%), in ankylosing spondylitis was type II (57.1%), in Fuchs' uveitis syndrome was type III (85.7%), in granulomatous uveitis was type V (42.9%), in infectious uveitis was type III (66.7), in JIA-associated uveitis was type I (66.7%). In eyes with idiopathic uveitis, several KP types were observed with no predominance of one KP type over the others (Table 2). The KP types showed a statistically significant difference between different uveitic syndromes (Fisher's exact test, $P<0.001$).

Careful analysis of corneal images obtained from participants included in this study revealed that in the overwhelming majority of the cases one or two types of KP types were present in the corneal endothelium. Occasionally, a third KP type could be seen, however, even in these cases they were few in number, small (types

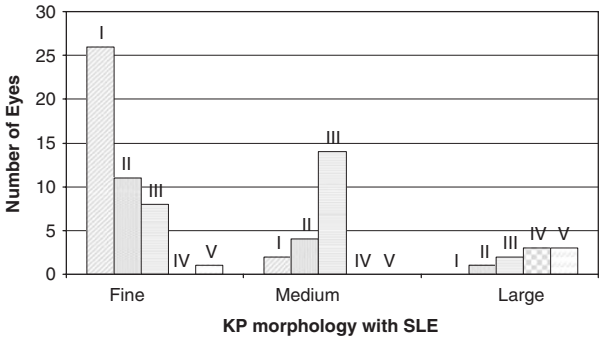

Figure 2 The association of keratic precipitate (KP) appearances as imaged with slit-lamp examination (SLE) and *in vivo* confocal microscopy (IVCM). Only primary KPs as imaged with IVCM have been included. The Roman numbers at the top of the bars refer to the KP types as imaged with IVCM.

I and II), and definitely did not amount to >10% of the total KPs. Even so, type IV and type V KPs were not observed at all in patients with Behçet's disease and JIA-associated uveitis.

Endothelial blebs were observed in several patients (Figure 1f). Blebs were visualized as empty lacunae within the endothelial cells with sizes ranging between 20 and 60 μm.

Discussion

Identification of the true nature of intraocular inflammation is especially of paramount importance in the management of uveitic disorders because the choice of specific treatment, be it systemic or local, anti-inflammatory or anti-infective, is dictated primarily by clinical findings obtained at the initial ocular examination that point to a certain aetiology. KPs are distinctive clinical findings that appear during the course of intraocular inflammation and limited suppositions as to the nature of the underlying uveitic disease may be made by the examination of KP morphology using slit-lamp biomicroscopy.[1] The paucity of studies on clinicopathologic correlation of KP stem from the fact that it is virtually impossible to obtain corneal samples during the course of active uveitis. However, the need to obtain more detailed information in the setting of uveitis has prompted the use of auxiliary instruments to image the KPs.[2,9] From a historical standpoint, KP morphology has been evaluated with specular microscopy in various studies.[9–12] The results of Pillai *et al*,[9] based on the findings of 13 patients with active unilateral uveitis, emphasized that the KP morphology may change over the course of uveitis, the endothelium surrounding the KP appeared abnormal and that the KP in Posner–Schlosman syndrome had a distinct, globular appearance. More recently, in a study by Wertheim *et al*,[2] IVCM has been utilized to evaluate the KP morphology and heterogeneity in 42 eyes of 33 patients with varying subtypes of uveitis including Fuchs' heterochromic iridocyclitis, HLA-B27-associated uveitis, granulomatous and infective uveitis. The results of that study pointed out KP appear more heterogeneous with IVCM compared to SLE, certain uveitic subtypes (infectious *vs* non-infectious) had distinct KP morphology and that the morphologic features of KP change during longitudinal follow-up.

In this study, KP morphology was evaluated in patients who had presented with active uveitis secondary to common uveitic syndromes. Overall, KP imaged with IVCM appeared to have more heterogeneous appearances than suggested by their SLE findings (Figures 1 and 2). Furthermore, in several (50 out of 75) eyes more than one type of KP was observed (Table 2). There was no noticeable difference in the appearance of KPs with respect to the region of the cornea imaged (zone of highest concentration *vs* a more peripheral location) in any of the patients. Our results support the findings by Wertheim *et al*[2] who also reported similar findings. In our study, fine KPs were more commonly associated with small, round (type I), and stippled (type II) KP types on IVCM, medium KPs corresponded to dendritiform (type III) KP, and large KPs were more commonly associated with larger (types IV and V) KPs. This observation leads to the conclusion that the KP size observed with SLE appears to be related to that imaged with IVCM. KP imaging with IVCM suggest that smaller KP types (types I and II) reflect single inflammatory cells and larger KP types (III and V) are more representative of multiple cell clusters.

One of the unique findings of our study concerns patients with Behçet's disease. Behçet's disease is a multisystem disorder with unknown aetiology characterized histopathologically by occlusive vasculitis.[13] Although infectious agents,[14] autoimmune mechanisms,[15] and genetic factors[14] have been implicated in the immunopathogenesis of Behçet's disease, the exact mechanism(s) remains obscure. The anterior and/or the posterior segment may be involved in Behçet's disease in the form of non-granulomatous intraocular inflammation. The non-granulomatous nature of the disease was reflected in this study by the paucity of large KP types on IVCM. In all patients with Behçet's disease, the predominant KP observed was of the small, round type (Table 2). The striking homogeneity of this KP type in Behçet's disease may have a potential clinical use in patients who present with anterior uveitis. Anterior uveitis with hypopyon may present features of both ankylosing spondylitis-associated uveitis and Behçet's disease.[1] In both of these conditions, fine KP are observed with SLE. Although stippled and small-round

KPs both appear as fine corneal deposits with SLE, they have different morphologic features with IVCM. IVCM may have a potential role in the differential diagnosis of these two conditions during an episode of acute active uveitis. In our study, as well as in the study by Wertheim *et al*,[2] the most frequently observed KP type with IVCM in patients with ankylosing spondylitis was that of the stippled type (Table 2).

This study also tried to identify whether certain KP were more frequently associated with infectious causes of uveitis when compared to non-infectious ones. Out of six eyes with infectious cause of uveitis, four (66.7%) had dendritiform KP (Table 2). In the study by Wertheim *et al*,[2] out of the nine cases with various infectious causes of uveitis, five (55.5%) had dendritiform KP with IVCM. On the other hand, none of the 24 eyes with non-infectious causes of uveitis had evidence of dendritiform KP. The authors of that article concluded that the observation of dendritiform KP may be more suggestive of an infectious cause of uveitis. The dendritiform appearance of KP in infectious causes of uveitis correspond to the histopathological findings in one case of HIV-associated cytomegalovirus retinitis in which chains of dendritiform macrophages linked by fibrin were observed on the corneal endothelium.[12] Although the findings of this study partially agree with those of the previous study by Wertheim *et al*,[2] dendritiform KP were also observed in non-infectious causes of uveitis such as in ankylosing spondylitis and idiopathic uveitis. Based on these results, we conclude that dendritiform KP are not specific for infectious uveitis and may also be observed in non-infectious uveitis syndromes.

Fuchs' uveitis syndrome is characterized by a chronic low-grade inflammation accompanied by medium-sized stellate type KP as observed with slit-lamp biomicroscopy.[3] In this study, the typical stellate KP of Fuchs' uveitis syndrome revealed predominantly dendritiform KP when imaged with IVCM. The overwhelming majority (85.7%) of the primary KPs were dendritiform in appearance. Dendritiform KPs were accompanied by larger (type IV), globular (type V), and stippled (type II) KP in some corneas. An infectious cause for Fuchs' uveitis syndrome was hypothesized from early on in the 20th century and included aetiologic agents such as herpes simplex virus[16] and *Toxoplasma gondii*.[17] However, recent evidence points out to a chronic rubella infection as pointed out in several studies.[18–20] In that aspect, the presence of dendritiform KP may be especially significant in supporting the association between dendritiform KP morphology and an underlying infectious cause for uveitis.

Idiopathic uveitis is an umbrella term for intraocular inflammation with unidentifiable causes. A previous study on 1237 patients who presented with uveitis pointed out that a in a significant (83%) proportion of patients, the underlying cause can not be identified at the initial evaluation and that prolonged longitudinal follow-up is required until the other systemic components of an underlying disorder become clinically apparent.[21] Our findings support the heterogeneity of the underlying causes of uveitis in cases initially labelled as 'idiopathic', in that several different KPs were observed with IVCM.

Our limited observations in JIA-associated uveitis support the non-granulomatous nature of this uveitic disorder. Small and stippled KPs were observed in the corneas of these patients (Table 2). However, more JIA patients are required to be evaluated with IVCM before making stronger inferences.

In agreement with clinical observations, the majority (71.4%) of primary KPs observed in granulomatous uveitis were of the larger subtypes (types IV and V; Table 2). Clinically, most (six out of seven) cases had large KPs and one had a medium-sized KP. These findings suggest that KP size imaged with IVCM is related to those observed with SLE.

Although, type IV and type V KPs are similar in size (Figure 1), their appearance are distinctly different, a finding also supported in the study by Wertheim *et al*.[2] Globular KPs contain multiple hyper-reflective inclusions in a larger round cluster, giving the KP a conglomerate appearance. In certain cases, this globular core has additional dendritiform extensions. On the other hand type IV KPs appear dull with smooth and round borders, do not contain hyper-reflective inclusions, and are not associated with dendritiform extensions. In our study, no clinical parameter appeared to be associated with large smooth rounded (type IV) *vs* globular (type V) KPs. However, the stage of inflammation at which the KPs were imaged may be responsible for the difference appearances of types IV and V KPs. The KPs of all patients were imaged with IVCM at an early stage intraocular inflammation when the patients had initially presented for evaluation and before the institution of any medication such as topical corticosteroids. However, it is possible that these patients may have had active intraocular inflammation for a certain period of time before their presentation. The significance of the distinct structures of these KP remains to be determined with future clinicopathologic correlation studies.

Deposition of pigment and protein debris on the corneal endothelium may also be imaged with IVCM and may theoretically be confused with cell deposition. However, the size of neutrophils and leucocytes range between 12–15 and 6–18 μm, respectively,[22] and appear significantly larger than pigment and protein which typically have sizes between 1 and 2 μm as observed with IVCM (unpublished data). Therefore, it is our opinion

that the precipitates larger than 5 μm that were observed with IVCM were of cellular origin.

The lack of data on longitudinal follow-up with IVCM is the major shortcoming of this study. However, the data obtained is consistent in that IVCM was performed in all patients in the active phase of uveitis.

In conclusion, the findings of our study suggest that a more detailed evaluation of KP morphology can be made with IVCM. Certain KP types appear to be characteristic, though not pathognomonic, of various uveitic syndromes such as Behçet's disease and Fuchs' uveitis syndrome. IVCM may have a potential role in the diagnostic work-up of uveitic patients.

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