

# Clinical features of infectious posterior segment uveitis

Crystal Sin Yi Cheung, MD,\* Adam Jekielek, † Nupura Bakshi, MD, FRCSC,\*‡  
 Rajeev Muni, MD, FRCSC,\*‡ Filberto Altomare, MD, FRCSC,\*‡  
 Louise Giavedoni, MD, FRCSC,\*‡ Alan Berger, MD, FRCSC,\*‡  
 Larissa M. Matukas, MD, FRCPC,<sup>S,||</sup> David Wong, MD, FRCSC,\*‡  
 Larissa Derzko-Dzulynsky, MD, FRCS(C)\*‡

## ABSTRACT •

**Objective:** To assess the clinical findings and microbiology investigations in patients with suspected infectious posterior segment uveitis (PSU).

**Design:** Retrospective case study.

**Methods:** Between January and December 2014, medical records of 270 patients with PSU were reviewed. Baseline ocular examination, presumed and final diagnoses, microbiology investigations from aqueous or vitreous fluid, and peripheral blood were reviewed.

**Results:** Infectious PSU was suspected in 28 patients among 270 PSU cases (10.4%, 28/270), and 11 cases were of infectious origin (4.1%, 11/270). Six patients were immunocompromised: 5 patients in the confirmed infectious PSU group (45.5%, 5/11) and 1 in the confirmed noninfectious group (5.9%, 1/17;  $p = 0.002$ ). Initial visual acuity was  $1.8 \pm 0.35$  logMAR and  $0.9 \pm 0.23$  logMAR for patients with confirmed infectious and noninfectious PSU, respectively ( $p = 0.04$ ). Anterior chamber reaction was worse in patients with confirmed infectious PSU ( $1.8 \pm 0.49$ ) than confirmed noninfectious cases ( $0.5 \pm 0.1$ ;  $p = 0.003$ ). The frequency of chorioretinitis among patients with confirmed infectious and noninfectious PSU is 54.5% (6/11) and 11.8% (2/17;  $p = 0.03$ ), respectively. Onset of confirmed infectious uveitis was more acute ( $\leq 6$  weeks in duration) than noninfectious cases ( $p = 0.0015$ ). Among the 11 patients with positive blood culture or serology, 6 had anterior and vitreous chamber fluid analysis. The rate of positive cultures and PCR is 16.7% (1/6) for aqueous humour and 50% (3/6) for vitreous samples.

**Conclusions:** Clinical features more suggestive of infectious PSU include immunosuppression, worse initial visual acuity, acute onset, worse anterior chamber reaction, and chorioretinitis. Further studies are needed to enhance the diagnostic yields of aqueous and vitreous fluid analyses.

Uveitis is one of the leading causes of ocular morbidity in the working age population and accounts for 10%–15% of vision loss in the Western countries.<sup>1,2</sup> Prompt differentiation of infectious from noninfectious posterior segment uveitis is of major significance as these 2 disease entities have vastly different treatment and prognosis. However, posterior uveitis of infectious and noninfectious etiology may have similar clinical signs and symptoms at initial presentation.<sup>3,4</sup> Although aqueous and vitreous fluid analyses are useful adjuvants to confirming the etiology, such microbiology investigations are limited to larger centres, and the diagnostic yields of cultures and polymerase chain reaction (PCR) vary greatly in the literature, from 27% to 100%.<sup>5</sup> The objective of this case series is to assess the clinical findings and microbiology testing used in suspected infectious posterior uveitis.

## MATERIALS AND METHODS

Between January 1, 2014, and December 31, 2014, in total 270 consecutive patients were diagnosed with intermediate uveitis, posterior uveitis, or panuveitis (defined as

“posterior segment uveitis or PSU” in this study) at the Department of Ophthalmology at St. Michaels Hospital, Toronto, Ont. This study was approved by Research Ethics Board for this retrospective single-centred study. The ocular diagnostic features are helpful but highly variable with overlap between both noninfectious and infectious PSU. For the purpose of this study, “suspected infectious PSU” is defined as PSU where clinical suspicion for infectious etiology is high based on a combination of initial history, disease onset especially if acute, immune status, exposure and travel history, presence of retinitis, vasculitis, chorioretinal lesions, optic nerve swelling, any panuveitis or endophthalmitis, dense vitritis on ultrasonography findings, or delayed resolution to empirical therapy. “Confirmed infectious PSU” refers to suspected infectious PSU cases with the infectious etiology identified by blood culture, serology, or PCR. “Confirmed noninfectious PSU” cases had negative microbiology and inflammatory investigations. Cases were described as idiopathic when no identifiable cause was found following from inflammatory and microbiology investigations. Exclusion criteria were (i) presence of anterior uveitis

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<https://doi.org/10.1016/j.jcjo.2017.11.004>

ISSN 0008-4182/17

alone, (ii) isolated episcleritis or scleritis, (iii) isolated optic neuritis, (iv) presumed noninfectious uveitis, (v) post-operative uveitis, and (vi) traumatic uveitis.

Complete history and ophthalmological assessment was performed. Patients were analyzed for sex, age of onset, systemic diseases, immune status including human immunodeficiency virus (HIV), and use of immunosuppressive therapy. Visual acuity, intraocular pressures, laterality, uveitis grading and course based on SUN criteria, and dilated fundus findings were obtained for the initial and final visits during the study period.<sup>4</sup> Systemic work-up including both microbiology and radiologic investigations, and ocular fluid analyses were performed when clinically indicated. Initial clinical diagnoses and confirmatory etiology of uveitis were evaluated.

Diagnostic anterior chamber paracentesis was performed at the slit lamp in outpatient settings, after topical proparacaine hydrochloride, disinfection of ocular surface with povidone-iodine, and placement of sterile lid speculum. A 30-gauge needle on a 1 mL syringe was used to aspirate approximately 0.1–0.2 mL of aqueous humour.

Vitreous specimen was obtained during either tap-and-inject procedures or 23-gauge pars plana vitrectomies (PPV). Vitreous chamber paracentesis was performed at the slit lamp in outpatient settings, after topical anaesthesia and povidone iodine, and placement of sterile lid speculum. A 25- to 27-gauge needle attached to a 1 mL syringe was used to aspirate approximately 0.1–0.2 mL of vitreous at 3.5–4 mm from limbus. In cases where vitreous sample was obtained using

23-gauge transconjunctival sutureless PPV, a standard 3-port setup approach was used in the operating room. Vitreous sample of approximately 0.2–0.3 mL was first obtained without infusion using gentle manual aspiration into a syringe. Thereby undiluted vitreous was retrieved for analysis. Owing to the retrospective nature of this study, the quantity of aqueous or vitreous fluid aspirated was not consistently documented.

Due to the small quantities obtained in aqueous chamber paracentesis and vitreous tap, the physicians need to be selective in the microbiology analysis performed. For suspected bacterial or fungal infectious PSU, gram stains and cultures were performed on the aqueous or vitreous fluid. For patients with suspected ocular toxoplasmosis or viral retinitis, PCR was preferentially performed. If the initial microbiology results were negative and clinical suspicion remain high for infectious etiologies, or there was delayed resolution of PSU with initial therapy, vitreous samples were obtained for additional analysis.

Nuclei acid from 200 µL of aqueous or vitreous fluid was extracted manually using QIAamp DNA (Qiagen, Mississauga, Ont.) and eluted in 200 µL of molecular-grade water according to manufacturer's instructions. Multiplex real-time PCR (RealStar<sup>®</sup> alpha Herpes PCR; Altona Diagnostics, Hamburg, Germany) was performed for herpes simplex virus 1 and 2 (HSV1/2) and varicella zoster virus (VZV) according to manufacturer's instructions. PCR utilizing primers common to herpes virus family members, followed by restriction enzyme digestion, was performed for the detection of

**Table 1—Demographic and clinical characteristics of patients with suspected infectious posterior uveitis**

	Confirmed Noninfectious Posterior Uveitis	Confirmed Infectious Posterior Uveitis	<i>p</i>
Total number of patients	17	11	
Total number of eyes	26	14	
<b>Sex</b>			
Male	10 (58.8%)	9 (81.8%)	0.25
Female	7 (41.2%)	3 (27.3%)	0.36
Age, years	51.8 ± 17.2	54.7 ± 16.9	0.93
Proportion of unilateral cases	8 (47.1%)	8 (72.7%)	0.25
Proportion of immunocompromised patients	1 (5.9%)	5 (45.5%)	0.002
Visual acuity at initial visit (logMAR)	0.9 ± 0.23	1.8 ± 0.35	0.04
Visual acuity at last follow-up visit (logMAR)	0.63 ± 0.18	1.26 ± 0.33	0.08
<b>Uveitis grading<sup>*</sup></b>			
Anterior uveitis grade	0.5 ± 0.1	1.8 ± 0.49	0.003
Vitrinitis grade	1.16 ± 0.15	1.63 ± 0.38	0.18
<b>Location of uveitis<sup>*</sup></b>			
Intermediate	5 (29.4%)	2 (18.2%)	0.67
Posterior	5 (29.4%)	3 (27.2%)	1.00
Panuveitis	6 (35.3%)	7 (63.6%)	0.25
<b>Uveitis course<sup>*</sup></b>			
Chronic	11 (64.7%)	0	0.0009
Recurrent	3 (17.6%)	3 (27.3%)	0.65
Acute	3 (17.6%)	9 (81.8%)	0.0015
<b>Ocular findings</b>			
Hypopyon	1 (5.9%)	3 (27.3%)	0.26
Chorioretinitis	2 (11.8%)	6 (54.5%)	0.03
Vasculitis	5 (29.4%)	1 (9.1%)	0.35
Optic nerve swelling	1 (5.9%)	1 (9.1%)	1.00
<b>OCT findings</b>			
Presence of macula fluid	3 (17.6%)	2 (18.1%)	1.00
Presence of epiretinal membrane	8 (47.1%)	3 (27.3%)	0.43

OCT, optical coherence tomography.  
Frequency calculations are based on number of patients.  
<sup>\*</sup>Based on Standardization of Uveitis Nomenclature (SUN) Working Group criteria.<sup>4</sup>

Table 2—Ocular manifestations for patients with confirmed infectious uveitis.

Patient No.	Clinical History			Initial Examination			
	Presenting Symptoms	Recent Travel History (Within 6 Months)	Initial Visual Acuity (logMAR)	Anterior Chamber Uveitis Grading*	Vitritis Grading* & snowbanks	Chorioretinal Lesions or Retinitis	Optic Nerve Swelling? Yes
1	Flashes, photophobia, pain	None	0.6	1+	1+ vitritis with snowballs	None	Yes
2	Decreased vision	None	0.5	0.5+	0.5+	Focal chorioretinal lesion	No
3	Pain, decreased vision	None	3.0 (LP)	3+	3+	Focal chorioretinal lesion	No
4	Decreased vision, floaters	None	3.0 (HM)	0.5+	1+	Chorioretinitis	No
5	Decreased vision, pain	None	3.0 (HM)	4+	4+ (dense vitritis on ultrasonography)	Unable to assess due to dense vitritis	Unable to assess due to dense vitritis
6	Floaters	None	3.0 (HM)	2+	2+	Chorioretinitis	No
7	Decreased vision	None	0.2	0	1+	Focal chorioretinal lesion	No
8	Decreased vision, pain	None	3.0 (HM)	2+	2+	Chorioretinitis	No
9	Decreased vision, pain	None	1.0	4+	4+ (dense vitritis on ultrasonography)	Unable to assess due to dense vitritis	Unable to assess due to dense vitritis
10	Decreased vision, pain	Travelled to South America 4 months before symptom onset	3.0 (LP)	4+	4+ (dense vitritis on ultrasonography)	Unable to assess due to dense vitritis	Unable to assess due to dense vitritis
11	Decreased vision	None	0.7	0	1+	Focal chorioretinal lesion	No

LP, light perception; HM, hand motion.

\*Based on the uveitis grading scheme from the Standardization of Uveitis Nomenclature (SUN) Working Group.

Epstein-Barr virus (EBV) and CMV.<sup>6</sup> For molecular detection of toxoplasmosis, samples were sent to the National Parasitology Laboratory, Montreal, Canada.

Commercial software (SPSS version 21.0 for Windows; SPSS, Inc, Chicago, IL) was used for all statistical analyses. Descriptive statistics was reported as means and standard deviation for continuous variables. The  $\chi^2$  test was used to compare proportion of categorical variables. A  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

A total of 270 patients with intermediate uveitis, posterior uveitis, and panuveitis were identified between January 2014 and December 2014. The mean age of presentation was  $53.3 \pm 17.1$  years. Twenty-eight of the 270 patients (10.4%) had suspected infectious PSU. Ocular findings of suspected PSU include presence of retinitis, vasculitis, chorioretinal lesions, optic nerve swelling, any panuveitis or endophthalmitis, dense vitritis on ultrasonography findings, or delayed resolution to empirical therapy. Microbiology investigations confirmed an infectious origin in 11 patients (39.3%, 11/28). Demographic profiles and clinical characteristics of the 28 patients are shown in Tables 1 and 2. There was a greater proportion of immunocompromised patients in the confirmed infectious group (45.5%, 5/11) than the noninfectious group (5.9%, 1/17;  $p = 0.002$ ).

Panuveitis was the most common presentation in patients with confirmed infectious PSU (63.6%, 7/11; Tables 1 and 2). In contrast, the frequencies of intermediate uveitis, posterior uveitis, and panuveitis at initial presentation were similar (29.4%, 29.4%, and 35.3%) for patients with confirmed noninfectious PSU (Table 2). The most common etiology for confirmed noninfectious PSU was idiopathic (64.7%, 11/17 patients). Among patients with confirmed infectious PSU, the most common organisms were *Toxoplasma gondii*, *Treponema pallidum*, and *Klebsiella* spp. (each comprising of 18.1% [2/11] of confirmed infectious uveitis) (Table 3). Additional lower-frequency causes of infectious PSU were *Candida*, *Bartonella*, *Aspergillus*, Methicillin-sensitive *Staphylococcus aureus*, VZV, and EBV.

Visual acuity at first clinical visit was significantly worse for patients with confirmed infectious PSU ( $1.8 \pm 0.35$ ) than noninfectious PSU ( $0.9 \pm 0.23$ ;  $p = 0.04$ ; Table 1). Severity of anterior chamber reaction was also significantly worse in patients with confirmed infectious PSU ( $1.8 \pm 0.49$  logMAR) than confirmed noninfectious PSU ( $0.5 \pm 0.1$  logMAR;  $p = 0.003$ ). Chorioretinitis occurred more frequently in patients with confirmed infectious PSU (54.5%, 6/11) than in confirmed noninfectious cases (11.8%, 2/17;  $p = 0.03$ ). In addition, confirmed infectious PSU was more likely to present acutely (6 weeks or less in duration) (81.8%, 9/11;  $p = 0.0015$ ), whereas confirmed noninfectious PSU had a more chronic course (64.7%, 11/17;  $p = 0.0009$ ).

On optical coherence tomography (OCT), the presence of macular fluid was similar between patients with confirmed

**Table 3—Microbiology testing for patient with confirmed infectious posterior uveitis**

Patient No.	Immune Status (Reason for Immune Compromise)	Initial Presumptive Diagnosis	Organism Identified	Systemic Antimicrobial Received at Time of Ocular Fluid Aspiration	Blood or Tissue Culture, or Blood Serology	Aqueous Fluid		Vitreous Fluid	
						Gram Stain, Culture	PCR	Gram Stain, Culture	PCR
1	Immunocompetent	<i>Bartonella</i>	<i>Bartonella</i>	None	Positive <i>Bartonella</i> titre	Not performed	PCR performed but uninterpretable	Not performed	Not performed
2	Immunocompetent	Syphilis or tuberculosis	<i>Treponema pallidum</i>	None	TPPA reactive	Not performed	Not performed	Not performed	Not performed
3	Immunocompromised (systemic prednisone and infliximab for birdshot chorioretinitis)	Candida	<i>Candida albicans</i>	Voriconazole	<i>Candida</i> isolated from blood culture	Not performed	Not performed	Gram stain: occasional polymorphs seen, no bacteria seen Culture: no fungus isolated	Not performed
4	Immunocompromised (HIV)	Syphilis, tuberculosis, or acute retinal necrosis	<i>Treponema pallidum</i> & EBV	None	TPPA reactive	Not performed	EBV detected	Not performed	Not performed
5	Immunocompromised (chronic alcoholism and poorly controlled diabetes)	Endogenous endophthalmitis secondary to <i>Klebsiella pneumoniae</i>	<i>K. pneumoniae</i>	Ceftriaxone	<i>K. pneumoniae</i> isolated from liver abscess aspirate	Gram stain: moderate polymorphs, no bacteria seen Culture: No growth	Not performed	Gram stain: Many gram-negative bacilli Culture: <i>Klebsiella</i> spp. isolated	Not performed
6	Immunocompetent	Endogenous endophthalmitis secondary to <i>Aspergillus</i>	<i>Aspergillus</i>	Voriconazole	Aspirate <i>Aspergillus</i> sp. isolated from lung abscess	Gram stain: No polymorphs seen Culture: No growth	Not performed	Gram stain: No polymorphs seen Culture: No growth	Not performed
7	Immunocompetent	Toxoplasmosis	<i>Toxoplasma gondii</i>	None	Toxoplasma IgG reactive, IgM nonreactive Toxoplasma IgG reactive, IgM nonreactive	Not performed	Not performed	Not performed	Not performed
8	Immunocompetent	Syphilis, tuberculosis, or acute retinal necrosis	VZV and EBV	Cotrimoxazole, ceftriaxone, fluconazole		Not performed	Not performed	Gram stain: Not performed Culture: No growth	EBV and CMV detected
9	Immunocompromised (chronic alcoholism and poorly controlled diabetes)	Endogenous endophthalmitis secondary to MSSA	MSSA	Cefazolin, vancomycin	MSSA isolated from blood cultures	Gram stain: Occasional polymorphs seen, No bacteria seen Culture: No growth	Not performed	Gram stain: Occasional polymorphs seen, No bacteria seen Culture: No growth	Not performed
10	Immuno-compromised	Endogenous endophthalmitis secondary to <i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>	Ceftriaxone, metronidazole	<i>K. pneumoniae</i> isolated from liver abscess aspirate	Gram stain: Many polymorphs seen, No bacteria seen Culture: No growth	Not performed	Gram stain: Moderate polymorphs seen, No bacteria seen Culture: No growth	Not performed
11	Immunocompromised (HIV)	Toxoplasmosis reactivation (history of toxoplasmosis in the same eye)	<i>Toxoplasma gondii</i>	None	Toxoplasmosis IgG positive, IgM negative	Not performed	Not performed	Not performed	<i>Toxoplasma</i> sp. detected <i>Toxoplasma</i> sp. detected
Overall rates of positive culture or PCR, n (%)						1/6 (16.7)	3/6 (50)		

TPPA, *Treponema pallidum* particle agglutination assay; PCR, polymerase chain reaction; HIV, human immunodeficiency virus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; MSSA, methicillin-sensitive *Staphylococcus aureus*. "Not performed" indicates that the aqueous and/or vitreous fluid was not sent for microbiology analysis.

infectious PSU (17.6%, 3/11) and confirmed noninfectious PSU (18.1%, 2/11;  $p = 1.00$ ). The frequency of epiretinal membranes was not significantly different between the 2 groups: 47.1% (8/17) for confirmed infectious PSU and 27.3% for noninfectious PSU (3/11;  $p = 0.43$ ).

Eleven of 28 patients with suspected infectious uveitis had organisms identified on blood or tissue culture, or blood serology or PCR. Among these 11 patients, 6 patients underwent anterior and vitreous humour analysis. The rates of positive cultures or PCR were 16.7% (1/6) for aqueous humour and 50% (3/6) of vitreous samples. Plausible explanations for this low frequency of confirmed infectious PSU will be described in the following section.

## DISCUSSION

Patients with posterior uveitis of infectious and non-infectious etiologies generally have similar initial clinical presentation.<sup>3</sup> Establishing a diagnosis in cases of suspected infectious uveitis is often supplemented by microbiology investigations, including aqueous and vitreous humour analysis. To the best of our knowledge, this is the first case series to compare the clinical characteristics of confirmed infectious and noninfectious uveitis among patients with suspected infectious PSU.

The mean age of our study population at overall uveitis onset was  $53.3 \pm 17.1$  years. This was higher than previous studies with the mean age between 30 and 45 years.<sup>7-9</sup> This may be due to lack of pediatric population in our series. However, the mean age of disease onset of confirmed infectious uveitis is  $54.7 \pm 16.9$  years in our series and this is similar to the rates reported in the study by Engelhard et al.; patients with advanced age may be more immunocompromised.<sup>10</sup> In our series, a greater proportion of immunocompromised patients were found in the confirmed infectious uveitis group (45.5%) than in the noninfectious category (5.9%;  $p = 0.002\%$ ). The 3 most common infectious organisms were toxoplasmosis, syphilis, and *Klebsiella*, each accounting for 18.1% of the confirmed infectious uveitis cases. Similar to previous series, toxoplasmosis was often the most common causative agent of posterior uveitis. Toxoplasmosis, along with cytomegalovirus (CMV) retinitis and herpes zoster ophthalmicus, were found to occur at substantially higher rates in HIV patients than in non-HIV patients in a retrospective study by Hodge et al.<sup>11</sup> Interestingly, there were no cases of CMV retinitis, and only one possible case of acute retinal necrosis (ARN) was identified in our case series (patient 8 with panuveitis and chorioretinitis and positive vitreous PCR for VZV and EBV). The lack of CMV retinitis cases may be attributable to the small number of immunocompromised patients in our study ( $n = 6$ ). The incidence of ARN is extremely low: 1 case per 1.6–2.0 million population per year, and other cases of ARN may have presented to other tertiary referral centres during the 12-month period of our study.

Idiopathic PSU was found in 64.7% (11/17 patients) of confirmed noninfectious cases. This is comparable to the

rates reported in the current literature, which ranges from 14.6% to 69% in tertiary referral centres.<sup>12-14</sup> The greater rate of idiopathic noninfectious cases in our series may be secondary to improved control of systemic noninfectious diseases, and thus there is a reduced rate of ocular involvement. Also our patient series included patients with intermediate uveitis, which is more often idiopathic, compared to other series reporting only posterior and panuveitis cases. Recent literature also reported an increased incidence of idiopathic uveitis, and this was observed in Singapore over a 9-year period.<sup>12</sup>

A diagnosis of definitive infectious uveitis was established in 11 patients in our series, which accounts for 39.3% (11/28) of suspected infectious cases and 4.07% (11/270) of total posterior uveitis and panuveitis cases. The overall rate of confirmed infectious uveitis ranges from 7.5% to 44.4%; however, the prevalence described in the literature often included anterior uveitis.<sup>12,15</sup> In a retrospective study focusing on posterior uveitis in Singapore, Mi et al. reported that infectious etiology accounted for 44.1% of posterior uveitis and panuveitis,<sup>16</sup> with Dengue and presumed tuberculosis being the 2 most common diseases.<sup>16</sup> Given the difference of risk exposures between countries, comparison of our study finding to those in Singapore is difficult.

A common trend observed in epidemiology studies is a reduced incidence of infectious uveitis. Mi et al. described a significant downward trend of overall infectious uveitis between 2004 and 2012.<sup>12</sup> Similarly, the incidence of *Toxoplasma* infection reduced markedly from 7.5/1000 in 1980 to 2.4/1000 in 2010.<sup>17</sup> Improvement of systemic management of infectious diseases and reduced rate of secondary ocular involvement in developed countries may account for these trends observed.

PCR, serology, and culture of aqueous and vitreous humor are useful adjuncts in the diagnosis of infectious uveitis.<sup>5</sup> In our series, the rate of positive cultures or PCR was 16.7% for aqueous fluid (1/6) and 50% for vitreous humour (3/6) among patients with confirmed organisms on blood cultures, serologies, or PCRs. There is a trend toward greater yield with vitreous than aqueous fluid. This conclusion has been reported in the literature previously.<sup>18</sup> The low rate of positive aqueous humour PCR is likely secondary to the small volume of aqueous obtained, because approximately 200  $\mu\text{L}$  aqueous is required for multiplex herpes PCR alone (specifically HSV1/2, VZV, CMV, and EBV). In addition, Goldmann-Witmer coefficient (GWC) analysis can be used for detecting intraocular antibody production.<sup>3,5</sup> Use of both PCR and GWC may improve the diagnostic yield of infectious PSU; in particular, GWC analysis was more informative for ocular toxoplasmosis than viral disease.<sup>5</sup> In addition, animal models of experimental autoimmune uveitis (EAU) have demonstrated increased phagolysosome activation in macrophages in the retinal pigment epithelium and clearance of foreign antigens in uveitic eyes.<sup>19</sup> As such, the PCR yield in anterior chamber samples may be low due to the clearance of these posterior segment antigens. The study by

De Groot-Mijnes et al. has found that if PCR of the aqueous humor was used as the sole diagnostic tool for infectious uveitis, then the correct diagnosis of infectious etiology would have been missed in 34% of herpesvirus and 64% of toxoplasmic chorioretinitis.<sup>5,20</sup> Although vitreous sampling provides adequate volume for multiple analyses, it is more invasive and has higher complication rates.<sup>21</sup> As such, aqueous humor analysis is often the preferred initial investigation before vitreous sample.<sup>5</sup> Our series utilized only PCR for analyzing aqueous samples from patients with suspected toxoplasmosis- and viral-related PSU, and GWC was not used due to the availability at our centre. The amount of aqueous humour extracted might have been less than 100 µL and therefore insufficient for analysis, leading to false-negative results. Our results highlight the need to develop laboratory techniques and protocols to identify pathogens from small aqueous fluid samples.

*Klebsiella* has been associated with antigenic cross-reactivity with vitreous antigen and stimulate an immune-mediated uveitis rather than an infectious one.<sup>22,23</sup> This was observed in patients 5 and 10. Both had positive blood culture for *Klebsiella*, and the vitreous culture was positive for the former patient, but indeterminate for the latter (Table 3). This suggests that uveitis in the setting of confirmed systemic infectious pathogen may implicate either an infectious or immune-mediated cause.

In conclusion, our study showed that clinical suspicion for infectious etiology for PSU should be higher in the presence of history of immunodeficiency, worse visual acuity on initial visit, more acute presentation, worse anterior chamber reaction, and presence of chorioretinitis. Our data also suggest the need for establishing laboratory tools to enhance the yield of aqueous sample analysis to rapidly establish the precise pathogen of infectious uveitis and initiate early antimicrobial therapy.

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## Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

From the \*Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ont.; †Faculty of Arts and Sciences, Queens University, Kingston, Ont.; ‡Department of Ophthalmology, St. Michael's Hospital, Toronto, Ont.; §Division of Microbiology, St. Michael's Hospital, Toronto, Ont.; ¶Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ont.

Institution at which study was conducted: St. Michael's Hospital, Toronto, Ont.

Originally received May. 7, 2017. Final revision Oct. 30, 2017. Accepted Nov. 7, 2017

Correspondence to Larissa Derzko-Dzulynsky, MD, FRCS(C), Department of Ophthalmology and Vision Sciences, University of Toronto, St. Michael's Hospital, 61 Queen Street East, 8th Floor, Toronto, Ont. M5C 2T2; derzkodzulynsky@rogers.com