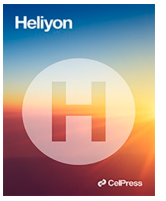
Heliyon 10 (2024) e39211

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Deciphering infectious uveitis etiology: Immune cell profiling in keratic precipitates using in vivo confocal microscopy

Fang Fang [a,b], Yanbing Wang [a,b], Yangyan Xiao [a,b], Huiling Li [a,b], Jiao Tian [a,b,*]

[a] Department of Ophthalmology, the Second Xiangya Hospital, Central South University, China
[b] Hunan Clinical Research Center of Ophthalmic Disease, Changsha, China

ARTICLE INFO

Keywords:
Keratic precipitates
Immune cells
Uveitis
Confocal microscopy

ABSTRACT

Purpose: To elucidate the etiology of infectious uveitis through the comprehensive analysis of keratic precipitates (KPs) using in vivo confocal microscopy (IVCM).
Design: Cross-sectional, observational case series.
Methods: This single-center, cross-sectional study was conducted at a tertiary care eye hospital from January 2021 to October 2023. It involved a detailed ophthalmologic evaluation of all subjects and included a total of 46 eyes from 36 subjects who were diagnosed with infectious uveitis. IVCM, specifically utilizing the HRT II Rostock corneal module, was employed to study the biomicroscopic morphology of KPs. The categorization of KPs was based on cell size, morphology, and reflection.
Results: Cells of KPs were assessed for size, morphology, and reflection through in vivo confocal microscopy. Patients, ranging in age from 13 to 80 years (median 51 years), exhibited diverse morphologic forms of KPs. Neutrophil-dominated KPs with uniform size were predominantly observed in bacterial and fungal endophthalmitis cases (19/19, 100 %), accompanied by small numbers of mononuclear-macrophages in three eyes (3/19, 15.8 %). Viral uveitis cases displayed a broader array of immune cell types, including characteristic striated or dendritic cells in all eyes (27/27, 100 %). Lymphocytes were commonly present (24/27, 88.9 %), forming clusters in sixteen eyes and dispersed in the corneal endothelium below the midline in eight eyes. Neutrophil infiltration was notable in three cytomegalovirus-infected eyes (3/27, 11.1 %). A marked increase in sub-basal corneal epithelial Langhans cells was associated with viral uveitis.
Conclusions: Neutrophil-dominated KPs strongly indicate endogenous bacterial or fungal endophthalmitis, while the presence of dendritic cells and lymphocytes in KPs is suggestive of viral uveitis. In vivo confocal microscopy emerges as a crucial tool for differentiating the etiologic diagnosis of infectious uveitis.

1. Introduction

Infectious uveitis accounts for a significant proportion of uveitis, which is one of the leading causes of visual impairment worldwide [1]. Common infectious causes of uveitis encompass endogenous infections like endophthalmitis, viral infections (including herpes simplex virus, herpes zoster virus, and cytomegalovirus), tuberculosis, syphilis, and parasite-related infections. Diagnosing uveitis

* Corresponding author. Department of Ophthalmology, the Second Xiangya Hospital, Central South University; Hunan Clinical Research Center of Ophthalmic Disease, No. 139 Renmin Road, Changsha, Hunan, 410011, China.
E-mail address: tianjiao001@csu.edu.cn (J. Tian).

https://doi.org/10.1016/j.heliyon.2024.e39211
Received 19 February 2024; Received in revised form 28 August 2024; Accepted 9 October 2024
Available online 10 October 2024

often presents challenges, but effective identification methods can improve diagnostic accuracy and treatment outcomes, ultimately enhancing prognosis.

The anterior chamber of the eye constitutes a unique microenvironment crucial for maintaining ocular health and function. In its normal state, this compartment lacks immune cells and fosters immune tolerance, a concept referred to as "immune amnesty" [2]. However, various ocular diseases can alter this microenvironment significantly. Inflammatory conditions such as uveitis and iritis can lead to immune cell infiltration into the anterior chamber, disrupting immune amnesty and triggering the release of inflammatory cytokines [3].

The human immune system comprises various cell types that collaborate in defense against infections and diseases. Extensive research has demonstrated that neutrophils, T cells, B cells, natural killer (NK) cells, dendritic cells, monocytes, and macrophages play distinct roles in immune defense and disease pathogenesis.

Keratic precipitates (KPs) represent characteristic features of uveitis, observed in the majority of uveitis cases. KPs are cellular deposits or aggregates on the corneal endothelium, primarily composed of epithelioid cells and immune cells [4]. Slit-lamp biomicroscopy remains the most common instrument for observing the morphological features of KPs. These precipitates can be classified based on their size when viewed under slit-lamp biomicroscopy, categorized as small, medium, or large. They can also be classified as granulomatous or nongranulomatous. Other morphological categories include stellate KPs and colored or pigmented KPs [4–6]. In the context of uveitis, the biomicroscopic appearance of KPs can offer valuable diagnostic clues for identifying the underlying inflammatory disorder [7].

In vivo confocal microscopy (IVCM) enables non-invasive imaging of the living human cornea, allowing for the detection of immune cells in the ocular anterior segment [8–10]. Recent studies evaluating morphologic patterns of KPs in various uveitis subtypes using IVCM have demonstrated its utility as an adjunctive tool for differentiating infectious from noninfectious uveitis [5,11,12] Notably, this technique reveals heterogeneity that is not easily discerned by conventional slit-lamp microscopy, holding diagnostic relevance. However, clinical observations highlight variability in KPs even within infectious uveitis, featuring distinct morphologies identified by IVCM based on etiology [13].

Moreover, KPs may manifest as single cells or as aggregates of multiple cells, exhibiting diverse morphologies. Determining the specific immune cell types within KPs and linking them to potential etiologies could significantly enhance our ability to categorize the type of uveitis.

The aim of this study was to use IVCM to compare the characteristics of KPs in infectious uveitis of different etiologies and to infer the type of immune cells based on the size, shape, and reflectivity of KPs. Smaller, uniformly sized cells are indicative of lymphocytes or neutrophils, larger round cells are usually macrophages, and dendritic or striated cells are dendritic cells. Reflectivity characteristics also aid in differentiation, with neutrophils displaying hyperreflective multilobed or S-shaped nuclei, while lymphocytes are uniformly mildly hyporeflective with occasional central punctate hyperreflectivity. Whether the immune cells were present singly or in clusters, we could observe them and comprehensively assess the cellular composition within KPs. These insights hold promise for improving diagnostic accuracy and optimizing therapeutic strategies in infectious uveitis.

2. Materials and methods

2.1. Participants

This cross-sectional observational study was conducted at the Second Xiangya Hospital, Central South University, from November 2021 to January 2023. Ethical approval was obtained from the Ethics Committee of the Second Xiangya Hospital, Central South University, adhering to the principles of the Declaration of Helsinki.

All enrolled patients underwent a comprehensive ophthalmologic assessment, including anterior and posterior segment evaluations, and systemic review conducted by a uveitis consultant. Images of KPs were taken at the patient's initial visit. Patients were excluded if there was a history of systemic glucocorticoid medication use or disease duration exceeded one month, because the morphologic features of KPs change during longitudinal follow-up [4].

2.2. Diagnostic criteria

Sixteen cases of bacterial and fungal endogenous endophthalmitis were diagnosed by a positive macrogenomic assay for vitreous pathogenic microorganisms. Additionally, two cases of fungal endophthalmitis were diagnosed by positive fungal cultures, and one case of bacterial endophthalmitis was diagnosed by a Gram-negative lipopolysaccharide test. Viral uveitis diagnosis was established when anterior chamber fluid or vitreous fluid tested positive for herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella-zoster virus (VZV), or cytomegalovirus (CMV) using fluorescent quantitative PCR.

2.3. IVCM and image analysis

IVCM was performed using the Heidelberg Retina Tomograph III Rostock Cornea Module (HRT III RCM; Heidelberg Engineering GmbH, Heidelberg, Germany). A single experienced examiner (TJ), proficient in this technique, conducted all examinations. Section scans of the corneal were captured with the Heidelberg HRT-III microscope, employing a field of view of 400 × 400 μm (384 × 384 pixels). Confocal images were obtained from the corneal epithelium to the anterior chamber, progressing from superficial to deep layers. To account for potential regional variations in KP morphology, images were acquired from the lowermost to the uppermost

region of the corneal endothelium.

Two observers (TJ and FF) experienced in corneal confocal microscopy worked together to screen images and identify immune cell types. The evaluators were not masked in this study, as the primary aim was to select images that offered sufficient clarity and to achieve consensus on cell identification. Only results where both observers agreed were included for cytometric measurement. The diameter of immune cells was measured using Image J software, with five well-structured cells of each immune cell type per eye chosen for measurement. This approach aimed to enhance precision in assessing the morphologic characteristics of KPs and the associated immune cell populations.

3. Rusults

A total of 46 eyes from 36 patients (10 women, 26 men) were evaluated in the study, with a mean age of 51.2 ± 18.5 years (range 13–80 years). Uveitis was unilateral in 26 subjects (72.2 %). The breakdown of uveitis etiologies revealed bacterial endophthalmitis in 10 eyes (22.2 %), fungal endophthalmitis in nine eyes (20.0 %), and viral uveitis in 27 eyes (57.8 %), including 11 eyes with CMV uveitis, eight eyes with HSV-1 uveitis, two eyes with HSV-2 uveitis, and six eyes with VZV uveitis.

Morphologically diverse keratic precipitates (KPs) were identified in the study series, encompassing neutrophils, monocytes-macrophages, dendritic cells, lymphocytes, and pigment clumps. Distinct immune cell types exhibited variations in morphology, size, reflectivity, relative distribution position, and aggregation patterns (Table 1, Fig. 1).

Infectious uveitis with different etiologies manifested specific cell types within KPs under in vivo confocal microscopy (Table 2). KPs in bacterial and fungal endophthalmitis predominantly featured neutrophils of uniform size (19/19, 100 %) (Fig. 2A–B), with three eyes (3/19, 15.8 %) showing a small number of mononuclear macrophages. Conversely, viral uveitis KPs displayed greater diversity in immune cell types. Striated or dendritic cells were present in all eyes (27/27, 100 %), and the majority of eyes (24/27, 88.9 %) exhibited lymphocyte predominance. Sixteen eyes (16/27, 59.3 %) displayed clustered lymphocytes (Fig. 3A–C), while others (8/27, 29.6 %) featured scattered lymphocytes below the middle of the corneal endothelium. Abundant neutrophil infiltration was notable in three CMV-infected eyes (3/27, 11.1 %) (Fig. 4A–C). Additionally, pigmented KPs were scattered in most eyes (20/27, 74.0 %), as confirmed by anterior segmental imaging.

In addition to the observation of KPs in the endothelial layer, we also noted that inflammatory cells in the subepithelial basal layer and filamentous fiber exudation in the anterior chamber differed in different etiologies (Table 3). Subepithelial basal neutrophils were characteristic findings in bacterial endophthalmitis but absent in fungal and viral uveitis. Bacterial and fungal uveitis exhibited Langham cells beneath the basal layer of the epithelium, albeit in small numbers. Conversely, viral uveitis demonstrated a spectrum ranging from a small to large number of Langham cells (Fig. 3B). Filamentous fiber exudation from the anterior chamber can be seen in bacterial and fungal uveitis (Fig. 2C), but not in viral uveitis.

4. Discussion

In this study, we leveraged the capabilities of in vivo confocal microscopy (IVCM) to delve into the intricate landscape of immune cells within keratic precipitates (KPs) in infectious uveitis, presenting a novel dimension to the diagnostic approach. While previous studies have utilized IVCM to observe KP morphology and classify KPs, this study extends the application to discerning specific immune cell types within KPs, providing a more nuanced understanding of the inflammatory processes [7,8,11,12].

The human immune system orchestrates a complex interplay of diverse cell types, in defense against infections and diseases. Neutrophils, T cells, B cells, natural killer (NK) cells, dendritic cells, monocytes, and macrophages, each with distinctive roles, form integral components of this defense mechanism.

Neutrophils, constituting the most abundant white blood cells, act as the first line of host defense against a spectrum of infectious pathogens [14]. Their distinct characteristics, including a segmented nucleus and susceptibility to degeneration in tissue inflammation, make them recognizable under confocal microscopy. Neutrophils tend to adhere flatly to the corneal endothelium due to their adhesion characteristics and, because they are usually denser than other immune cells, they are generally located toward the bottom of the anterior chamber [15,16].

Table 1
Characteristics of immune cell morphology and pigment presence in keratic precipitates of infectious uveitis with in vivo confocal microscopy.

Cell types in KPs	Shape	Size	Diameter (μm)	Reflective	Distribution	Aggregation Patterns
Neutrophils	Round or naked nuclei	Uniform	9.79 ± 1.34	Highly reflective Multilobed or S-shaped nuclei	Inferior	Clustered
Monocyte macrophages	Round or round-like	Significantly Larger	20.20 ± 4.04	Uneven medium to high reflection	Infero-central	Dispersed
Dendritic cells	Strip or dendritic	Varying in Size	59.42 ± 20.70	Medium Reflective	Superior	Crossed
lymphocytes	Round or round-like	Uniform	9.38 ± 1.84	Even medium-low reflection with intermittent high-reflection dots	Infero-central	Lumpy or Scattered
Pigment	irregular	Varying in Size	Not applicable	Uniform intense reflection	Infero-central	Not applicable

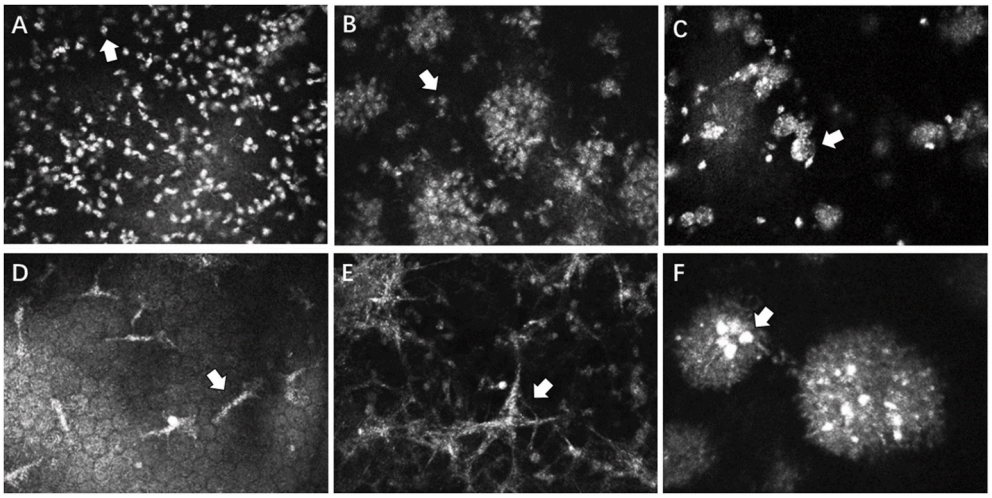


Fig. 1. Examples of various immune cell types and pigment within keratic precipitates (KPs) observed with in vivo confocal microscopy. A, Neutrophils: Round cells of uniform size with distinctive hyperreflective multilobed or S-shaped nuclei; B, Monocytes-Macrophages: Rounded or nearly round cells, notably larger than other cell types, exhibiting heterogeneous moderately hyperreflective; C and D, Dendritic Cells: Striped or dendritic shapes, varying in size and thickness, generally exhibiting medium reflectivity; E, Lymphocytes: Round or nearly round cells; this image depicts uniform-sized cells, while other infiltrates might include both large and small lymphocytes. Lymphocytes typically are uniformly mildly hyporeflective with occasional central punctate hyperreflectivity; F, Pigment Clumps: Highly hyperreflective clumps of varying sizes, often embedded in larger KPs.

Table 2
Distribution of various immune cell types and pigment presence in keratic precipitates of infectious uveitis caused by different Pathogens observed by in vivo confocal microscopy.

Cell types in KPs	Bacteria	Fungi	Hsv-1	Hsv-2	CMV	VZV
Neutrophils	10	9	0	0	3	0
Monocyte macrophages	3	0	0	0	2	3
Dendritic cells	0	0	8	2	11	6
lymphocytes	0	0	8	2	8	6
Pigment	0	0	7	1	6	6

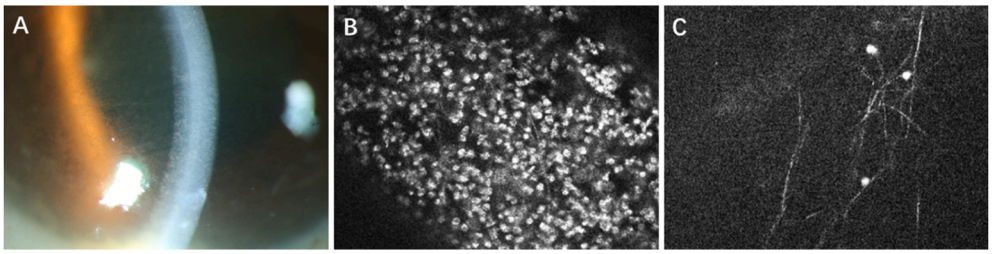


Fig. 2. Representative images of the anterior segment of a patient (Case A-57) with bacterial endophthalmitis. A, Standard slit-lamp photograph displaying diffuse fine KPs in the anterior chamber; B, In vivo confocal microscopy (IVCM) image showing a significant number of neutrophils on the corneal endothelial surface; C, IVCM image revealing fibrous exudate in the anterior chamber.

Lymphocytes, the smallest immune cells, account for a significant portion of white blood cells. Their tendency to aggregate leads to the formation of KP clusters, typically distributed in the middle and lower parts of the corneal endothelium [17]. The subtypes of T, B, and NK cells circulate in the peripheral blood, contributing to cell-mediated immunity, antibody production, and direct killing of infected cells, respectively [18].

Monocytes, comprising 2 %–10 % of all leukocytes, can differentiate into macrophages and dendritic cells. Macrophages, through phagocytosis nature, play a critical role in innate immunity, tissue repair, and immune regulation [19]. The overlap in morphology and size between monocytes and macrophages classifies them together as mononuclear-macrophages under in vivo confocal microscopy [20].

Dendritic cells (DCs), specialized white blood cells, bridge the innate and adaptive immune systems. Their characteristic branched

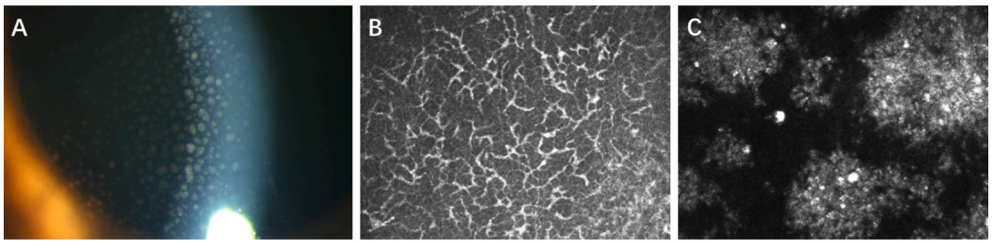


Fig. 3. Representative images of the anterior segment of a patient (Case A-44) with varicella-zoster virus (VZV) uveitis. A, Standard slit-lamp photograph displaying large KPs in the anterior segment of the left eye; B, IVCM image exhibiting a substantial presence of Langhans cells beneath the basal layer of the corneal epithelium; C, IVCM image revealing clustered lymphocytes interspersed with pigmented KPs.

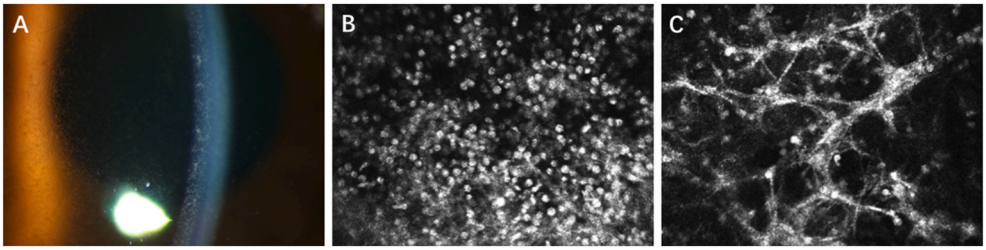


Fig. 4. Representative images of the anterior segment of a patient (Case A-36) with cytomegalovirus (CMV) uveitis. A, Standard slit-lamp photograph displaying dusty KP below the corneal endothelium, transitioning to striped KP above in the anterior segment of the right eye; B, IVCM image showing a considerable presence of neutrophils on the bottom of the corneal endothelium; C, IVCM images showing the presence of large numbers of dendritic cells on the upper area of the corneal endothelium interspersed with scattered neutrophils and lymphocytes.

Table 3
In vivo confocal microscopy analysis of immune cells in the subepithelial basal layer and filamentous fiber exudation in the anterior chamber of the infectious uveitis cases.

Pathogens	Bacteria	Fungi	Virus
Subepithelial basal neutrophils	4/10	0	0
Subepithelial basal Langham cells	2/10	3/9	14/27
filamentous fiber exudation in the anterior chamber	4/10	3/9	0

morphology aligns with the long striped or dendritic appearance observed in KPs [21,22]. The upper part of the endothelium is a key area for detecting dendritic cells within KPs. Langham cells also tend to adsorb lymphocytes and together they form a clumped KP.

Endogenous bacterial and fungal endophthalmitis, marked by the infiltration of neutrophils, monocytes, and macrophages, aligns with the histopathological findings of the disease. Early involvement of neutrophils and subsequent recruitment of monocytes and macrophages are consistent with previous reports on bacterial and fungal endophthalmitis [23–26].

Viral uveitis, a sight-threatening condition, involves a diverse immune response, notably featuring T cells as the predominant cell type. The immune response to viral infection in the anterior chamber involves the accumulation of various immune cells, such as lymphocytes, macrophages, and dendritic cells [27,28]. The observed variation in immune cell composition within KPs, particularly the predominance of neutrophils in cytomegalovirus (CMV) cases, may reflect the immunocompromised status or the early immune response in these patients [29–31] Freshly pigmented KPs are usually present in conjunction with inflammatory cells and are commonly seen in viral uveitis [4].

Subbasal corneal epithelial Langhans cells, often associated with viral keratitis, were notably present in viral uveitis cases, particularly in the periphery of the cornea [32]. Their increased visibility may serve as an indicator of intraocular viral infection.

The presence or absence of fibrous exudate in the anterior chamber, discerned through IVCM, offers additional diagnostic clues, potentially distinguishing bacterial and fungal endophthalmitis from viral uveitis.

The present study has several limitations. The inability to extract KPs for further examination limits the precision in interpreting cell size and morphology. Further distinctions between large and small lymphocytes were not feasible. Additionally, uncommon infectious uveitis cases, such as tuberculous uveitis and ocular toxoplasmosis, were not extensively explored.

In conclusion, in vivo corneal confocal microscopy effectively differentiates immune cell types within KPs. Distinct patterns observed in various infectious uveitis cases correspond to the pathological states of the diseases, enhancing diagnostic capabilities. Future research can leverage this technique to explore additional immune cell types and dynamic processes in ocular inflammatory diseases, bridging the gap between clinical and basic research.

CRediT authorship contribution statement

Fang Fang: Writing – review & editing, Funding acquisition, Formal analysis, Data curation. **Yanbing Wang:** Project administration, Investigation. **Yangyan Xiao:** Project administration, Investigation. **Huiling Li:** Writing – review & editing, Supervision, Methodology. **Jiao Tian:** Writing – original draft, Conceptualization.

Ethics declarations

This study did not involve patient privacy or identifiable information. The Hospital Medical Ethics Committee granted a waiver for informed consent, and therefore, formal approval was not necessary.

Data availability statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Funding

This work was supported by Natural Science Foundation of Hunan (2023JJ10087), Natural Science Foundation of Changsha (kq2208297), and Health Commission of Hunan Province (W20242010) which were the source of funding for this study.

Declaration of competing interest

No conflict of interest exits in the submission of this manuscript.

References

[1] E. Miserocchi, et al., Review on the worldwide epidemiology of uveitis, Eur. J. Ophthalmol. 23 (5) (2013) 705–717.
[2] J.W. Streilein, Ocular immune privilege: therapeutic opportunities from an experiment of nature, Nat. Rev. Immunol. 3 (11) (2003) 879–889.
[3] J.T. Rosenbaum, et al., Endotoxin-induced uveitis in rats as a model for human disease, Nature 286 (5773) (1980) 611–613.
[4] M.S. Wertheim, et al., In vivo confocal microscopy of keratic precipitates, Arch. Ophthalmol. 122 (12) (2004) 1773–1781.
[5] P. Mahendradas, et al., In vivo confocal microscopy of keratic precipitates in infectious versus noninfectious uveitis, Ophthalmology 117 (2) (2010) 373–380.
[6] R.V. Agrawal, et al., Current approach in diagnosis and management of anterior uveitis, Indian J. Ophthalmol. 58 (1) (2010) 11–19.
[7] M.C. Mocan, S. Kadayifcilar, M. Irkec, Keratic precipitate morphology in uveitic syndromes including Behcet's disease as evaluated with in vivo confocal microscopy, Eye (Lond) 23 (5) (2009) 1221–1227.
[8] D.V. Patel, J. Zhang, C.N. McGhee, In vivo confocal microscopy of the inflamed anterior segment: a review of clinical and research applications, Clin. Exp. Ophthalmol. 47 (3) (2019) 334–345.
[9] A. Zhivov, et al., In vivo confocal microscopy of the ocular surface, Ocul. Surf. 4 (2) (2006) 81–93.
[10] R.L. Niederer, C.N. McGhee, Clinical in vivo confocal microscopy of the human cornea in health and disease, Prog. Retin. Eye Res. 29 (1) (2010) 30–58.
[11] L.L. Lim, et al., In vivo laser confocal microscopy using the HRT-rostock cornea module: diversity and diagnostic implications in patients with uveitis, Ocul. Immunol. Inflamm. 26 (6) (2018) 900–909.
[12] M.R. Kanavi, M. Soheilian, N. Naghshgar, Confocal scan of keratic precipitates in uveitic eyes of various etiologies, Cornea 29 (6) (2010) 650–654.
[13] N.S. Chan, S.P. Chee, Keratic precipitates: the underutilized diagnostic clue, Ocul. Immunol. Inflamm. (2021) 1–10.
[14] T.N. Mayadas, X. Cullere, C.A. Lowell, The multifaceted functions of neutrophils, Annu. Rev. Pathol. 9 (2014) 181–218.
[15] A. Mantovani, et al., Neutrophils in the activation and regulation of innate and adaptive immunity, Nat. Rev. Immunol. 11 (8) (2011) 519–531.
[16] M.D. Filippi, Neutrophil transendothelial migration: updates and new perspectives, Blood 133 (20) (2019) 2149–2158.
[17] D.E. Lewis, G.R. Harriman, S.E. Blutt, Organization of the immune system. Clinical Immunology, 2008.
[18] D.F. Larosa, J.S. Orange, 1. Lymphocytes, J. Allergy Clin. Immunol. 121 (2 Suppl) (2008) S364–S369, quiz S412.
[19] Y. Oishi, I. Manabe, Macrophages in inflammation, repair and regeneration, Int. Immunol. 30 (11) (2018) 511–528.
[20] A.A. Patel, F. Ginhoux, S. Yona, Monocytes, macrophages, dendritic cells and neutrophils: an update on lifespan kinetics in health and disease, Immunology 163 (3) (2021) 250–261.
[21] B. Bosnjak, et al., Imaging dendritic cell functions, Immunol. Rev. 306 (1) (2022) 137–163.
[22] R.M. Steinman, Z.A. Cohn, Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution, J. Exp. Med. 137 (5) (1973) 1142–1162.
[23] M.C. Callegan, et al., Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions, Clin. Microbiol. Rev. 15 (1) (2002) 111–124.
[24] M.J. Giese, et al., Mitigation of neutrophil infiltration in a rat model of early Staphylococcus aureus endophthalmitis, Invest. Ophthalmol. Vis. Sci. 44 (7) (2003) 3077–3082.
[25] R.T. Ramadan, et al., Acute inflammation and loss of retinal architecture and function during experimental Bacillus endophthalmitis, Curr. Eye Res. 31 (11) (2006) 955–965.
[26] F.C. Miller, et al., Targets of immunomodulation in bacterial endophthalmitis, Prog. Retin. Eye Res. 73 (2019) 100763.
[27] J.D.F. De Groot-Mijnes, et al., Immunopathology of virus-induced anterior uveitis, Ocul. Immunol. Inflamm. 26 (3) (2018) 338–346.
[28] G.M. Verjans, et al., T cells specific for the triggering virus infiltrate the eye in patients with herpes simplex virus-mediated acute retinal necrosis, J. Infect. Dis. 178 (1) (1998) 27–34.
[29] G.A. Mora Scarpetta, et al., Evidence for the involvement of interleukin-1 alpha during development of experimental cytomegalovirus retinitis in immunosuppressed mice, Cytokine 144 (2021) 155596.
[30] H. Chien, R.D. Dix, Evidence for multiple cell death pathways during development of experimental cytomegalovirus retinitis in mice with retrovirus-induced immunosuppression: apoptosis, necroptosis, and pyroptosis, J. Virol. 86 (20) (2012) 10961–10978.
[31] G. Tummala, et al., Characterization of gene therapy associated uveitis following intravitreal adeno-associated virus injection in mice, Invest. Ophthalmol. Vis. Sci. 62 (2) (2021) 41.
[32] R.M. Peng, et al., Characteristics of corneal endotheliitis among different viruses by in vivo confocal microscopy, Ocul. Immunol. Inflamm. 29 (2) (2021) 324–332.