• Review Article •

A novel terminologic "naming-meshing" system using anterior chamber sedimentation for early diagnosis and prompt treatment of ocular or systemic diseases: is it hypopyon or pseudohypopyon?

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Received: 2022-12-23 Accepted: 2023-06-02

Abstract

• A novel, algorithmic "naming-meshing" system was introduced for the distinction of hypopyon from pseudohypopyon to make an early diagnosis and prompt treatment of anterior chamber collection standardized to encompass all sediment characteristics. For this reason, a literature review of "hypopyon" and "pseudohypopyon" was conducted in MEDLINE/PubMed, Scopus, and Web of Science from 1966 to May 15, 2023. Two issues were clarified: 1) which strategies should the ophthalmologist follow when asked to evaluate an eye with anterior chamber sedimentation to distinguish hypopyon from pseudohypopyon, and 2) in which systemic disorders should a non-ophthalmologist order a prompt ophthalmic consultation to distinguish pseudohypopyon from hypopyon. Pathognomonic characteristics of the sediment were examined; scleral show (warm/cold), location (corneal/anterior chamber/capsular/posterior), visibility (macro/micro/occult-angle), orientation (horizontal/vertical/oblique), number (single/double), shape (convex/triangular/pyramidal/ring/lumpy/inverse), and color (white/yellow/pink/brown/black). Associated findings were then assessed; acute/chronic, spontaneous/provoked, unilateral/bilateral, inflammatory/non-inflammatory, suppurative (non-sterile)/non-suppurative (sterile), granulomatous/non-granulomatous, recurrent/non-recurrent, shifting/non-shifting, and transient/persistent. The type of precipitation was *named* (naming) and *matched* (meshing) to a potential list of etiologies (inflammatory, infective, therapeutic, masquerades). Given that (pseudo)hypopyon predominantly afflicts younger patients in their most productive years, clinicians supervising such patients should be aware of all sediment characteristics. The ophthalmologist should never ask non-ophthalmologists to run the full battery of tests in a patient with (pseudo)hypopyon, and rather indicate which type of collection is present, what its pathognomonic feature is, and what the most likely diagnoses to be excluded are.

• **KEYWORDS:** naming-meshing; hypopyon; pseudohypopyon
DOI:10.18240/ijo.2023.08.21

Citation: Evereklioglu C, Sener H, Sonmez HK, Polat OA, Gulmez Sevim D, Arda H, Horozoglu F. A novel terminologic "naming-meshing" system using anterior chamber sedimentation for early diagnosis and prompt treatment of ocular or systemic diseases: is it hypopyon or pseudohypopyon? *Int J Ophthalmol* 2023;16(8):1337-1349

INTRODUCTION

"Hypopyon" and "pseudohypopyon", layered sediment formations in the dependent part of the eye, are etiological terms defining respectively the inflammatory or non-inflammatory origin of the precipitates in ocular or systemic diseases[1]. Since the first clinical use of the term "hypopyon" centuries ago[2], non-standardized diagnostic definitions by clinicians have led to either confusion or misuse of terms in scientific publications in an attempt to describe the true nature of the collection in the eye. However, the distinction of "hypopyon" from "pseudohypopyon" is essential for a physician and prompt diagnosis of the underlying etiology of the collection is of utmost importance to prevent sight- and life-threatening ocular or systemic complications, which carry a poor prognosis if not addressed at the earliest because their management and prognosis are completely different.

In general, most uveitis specialists treat hypopyon as a finding. However, it is in fact a disease entity in many ways and there is no nomenclature system that can be used by

both ophthalmologists and other clinicians for differential diagnosis of this unique finding, which takes into account various pathognomonic characteristics of the scleral show and the precipitation, such as the onset, chronicity, visibility, orientation, laterality, recurrency, mobility, location, color, shape, number, sterility, behavior, and course, indicating the most likely etiological diagnosis.

This article outlines the pathognomonic features of "hypopyon" and "pseudohypopyon" in any part of the eye regarding the underlying infectious or non-infectious inflammatory etiologies and masquerading syndromes to plan the interaction among ophthalmologists, dermatologists, rheumatologists, internists, and pediatricians.

MATERIALS AND METHODS

This review article was conducted in PubMed/MEDLINE, Scopus, and Web of Science from 1966 to May 15, 2023 by searching the words of uveitis, hypopyon, pseudohypopyon, Behçet, and HLA-B27, our own published papers, and manual searches based upon articles cited in the texts of other articles. Many of the relevant full articles were obtained by personal communication with relevant authors, or downloaded in PDF format, where available. Papers were included if they came from peer-reviewed journals. Institutional review board approved the study (approval number: 30052023/76).

Two issues were clarified: 1) which strategies should the ophthalmologist follow when asked to evaluate an eye with anterior chamber sedimentation to distinguish hypopyon from pseudohypopyon, and 2) in which systemic disorders should a non-ophthalmologist order a prompt ophthalmic consultation to distinguish pseudohypopyon from hypopyon.

Therefore, a novel, up-to-date, and stepwise classification guideline was constructed and standardized based on an algorithmic "naming-meshing" system (Table 1)[1-45]. By using this scheme, physicians can recognize the character of the sediment correctly, make detailed descriptions, narrow their differential diagnosis in a systematic manner, assist in targeted investigations for laboratory work-up, and finally diagnose the etiology on time for referral to the relevant clinician and prompt treatment.

RESULTS

Terminology "Hypopyon" when used alone classically indicates inflammatory sediment formation in the anterior chamber of the eye and signifies an advanced exudative stage of an acute eye condition that causes pericorneal injection with ocular pain, decreased vision, photophobia, and lacrimation, indicating severe intraocular inflammation that rapidly responds to corticosteroids[1]. It is intimately related to the breakdown of the blood-aqueous barrier of the iris and the ciliary body capillaries, resulting in increased permeability of the nonpigmented ciliary epithelium, posterior iridial epithelium, and the endothelial cells of the iris. During the active stage of the disease, hypopyon contains abundant influx of recruited inflammatory white blood cells from the surrounding uveal tissues into the anterior chamber of the eye, mainly polymorphonuclear leukocytes, as the first and most active cells, necrotic tissue debris, proteins, fibrin, inflammatory mediators, microbial agents (if infective) and by-products, with a late arrival of lymphocytes. The most common forms of "non-infectious hypopyon" (sterile inflammation) in the anterior chamber are ocular Behçet disease (OBD) and HLA-B27-related acute anterior uveitis (AAU), whereas exogenous or endogenous suppurative endophthalmitis is the most frequent etiologies of "infectious hypopyon", which is associated with increased risk of sight-threatening complications or vision loss.

"Pseudohypopyon" defines non-inflammatory, long-standing, and painless precipitations in the anterior chamber of the eye, which are commonly observed in ocular or systemic "masquerade syndromes of malignancy", and does not or only minimally responds to corticosteroids[3]. Various terms such as "non-infective hypopyon", "tumor-associated hypopyon", "malignant hypopyon" or "neoplastic hypopyon" have been used in the literature to define these collections. However, it is not etiologically a sedimentation of inflammatory origin and, therefore, the eponym "pseudohypopyon" or, strictly speaking, "tumoral/neoplastic pseudohypopyon" should be strongly preferred once the diagnosis is established, since anterior chamber "pseudohypopyon" does not always develop as a result of ocular or systemic malignancies. Similarly, although the clinical appearance of "pseudohypopyon" is identical in general with those seen in "inflammatory sterile hypopyon", the use of "non-inflammatory hypopyon" for such precipitation would not exactly define its true nature since "tumoral pseudohypopyon" may still have an associated inflammatory component in some cases from its traumatic or destructive effect on the uvea. The collection contains neoplastic cells mainly from leukemia, lymphoma, and retinoblastoma without any microbial agent or pus[4]. Leukemia is the most common systemic malignancy that can produce metastasis to the eye whereas vitreoretinal lymphoma is the most common intraocular lymphoproliferative disease due to metastasis from systemic lymphoma[5]. Retinoblastoma, on the other hand, accounts for the most common intraocular tumor in small children under 3 years old and presents mostly with leukokoria[6]. The eye in pseudohypopyon is white without pericorneal injection or uveitic symptoms and signs, though repetitive head shaking or chronicity of the disorder may result in mild inflammatory reactions along with secondary uveitis due to neoplastic cell irritation of the uveal tissues, as stated above.

Table 1 "Naming-meshing" system for sediment formation in the dependent part of the eye (observational, behavioral, locational, and etiopathologic definition of precipitations' characteristics)[1-45]

Naming	Definitions-characteristics-frequency	Meshing (etiology)
1. Sex-age[1-6]		
Male	In general, hypopyon occurs more frequently in men from any cause between 20 and 40y	HLA-B27-related AAU, OBD
Female	HLA-B27-related AAU is the most common cause of hypopyon uveitis; hypopyon occurs more frequently in women than men in OBD	HLA-B27-related AAU, OBD
2. Formation[1,3,7-9]		
Hypopyon		
Spontaneous	From intraocular inflammation	OBD, HLA-B27-related AAU
Provoked	Induced by local trauma	After intraocular surgery
Pseudohypopyon		
Spontaneous	From neoplastic collections	Masquerade syndromes (leukemia, lymphoma)
3. Visibility[1,3-5,8-28]		
Macro-(pseudo)hypopyon	Externally visible to the naked eye or may be seen only on downgaze in some cases	Collections from various etiology (HLA-B27-related AAU, OBD, masquerade syndromes)
Micro-(pseudo)hypopyon	Visible on slit-lamp biomicroscopy (may circulate in the anterior chamber)	Similar to macro-(pseudo)hypopyon
Angle/occult-(pseudo)hypopyon	Visible on gonioscopic examination only (possibly the most common form)	Similar to macro-(pseudo)hypopyon
4. Orientation[1,8-9,29]		
Hypopyon		
Horizontal	The classic form of layered sediment formation inferiorly at the 6 o'clock position in the upright posture that is heaped up, if present, at its edges	OBD, HLA-B27-related AAU
Vertical/oblique	Non-horizontally layered sediment formation	OBD, long-term bedridden patients,
Pseudohypopyon		
Horizontal	The classic form in the upright posture	Masquerade syndromes
Vertical/oblique	Upon leaning to one side or head-tilt test	Masquerade syndromes
5. Shape & position[1-9,27,30-37]		
Hypopyon		
Boat-shaped	Crescent-shaped hypopyon with elevated edges	Fungal endogenous endophthalmitis
Convex or triangular	Sediment that is typically heaped up centrally rather than at its edges	Microbial keratitis, rarely in HLA-B27-related AAU
Pyramidal	Sediment that is characteristically heaped up centrally with prominent geographical corneal infiltration and satellites	Fungal keratitis
Ring	A curved collection	Meningococcal endophthalmitis
Inverse (upside-down)	An exudate layered superiorly at the 12 o'clock position	Infectious scleritis
Pseudohypopyon		
Lumpy, wavy	Sediment that has a "zigzag" shape rather than a classical layered collection	Tumoral pseudohypopyon
Inverse/inverted/reverse (hyperoleon)	Anterior or posterior chamber whitish collection layered superiorly as a feature of emulsified silicone oil tamponade, which is lighter than aqueous humor	Post-vitrectomy, management of retinal detachment
6. Color (hue)[1,4-6,15-26]		
Hypopyon		
White (grayish-white)	The usual form of sediment	OBD, HLA-B27-related AAU
Pink-colored	In the absence of hyphema	Pigment-producing Enterobacteriaceae *Serratia marcescens* or staphylococcus aureus-endophthalmitis
Candy-cane	A small hypopyon mixed with hyphema	HSV and VZV
Darkly-pigmented	Pigment dispersion of melanin granules from necrotic iris into the anterior chamber with a darkening from tan to black	*Listeria monocytogenes- and Serratia marcescens*-induced endogenous endophthalmitis, intraocular tuberculosis
Pseudohypopyon		
White (dirty-white)	The usual form of sediment that may be grayish-white in appearance	Metastatic or primary intraocular tumors
White crystalline	Sediment containing steroid crystals that mimic pseudoendophthalmitis	After IVTA injection
Yellow-colored	Sediment containing steroid or gold cholesterol crystals (its crystalline structure is seen by high magnification biomicroscopy)	Cholesterolosis bulbi, after IVTA injection
Brown-colored	Sediment with hemolytic changes	Erythrocyte "ghost cells" glaucoma
Blood-tinged (pinkish)	Tumoral cells layered in the anterior chamber as a blood-streaked collection	Spontaneous hemorrhagic neoplastic cells from ocular lymphoma or leukemia
Black-colored	Composed of pigment-laden macrophages and neoplastic melanoma cells	Metastatic or primary uveal necrotizing melanomas
7. Mobility[1,3-9]		
Hypopyon		
Shifting (within minutes)	Total gravitational dislocation of the sediment into another position upon postural change or head tilting test (contains a lower level of fibrinous exudate)	OBD (pathognomonic finding)
Non-shifting (plastic)	Plastic hypopyon that is immobile despite permanent postural change (contains a higher level of fibrinous exudate)	HLA-B27-related AAU, infectious endophthalmitis, leptospirosis
Pseudohypopyon		
Shifting (within seconds)	Dispersion of sediment with a head shake or its total gravitational dislocation into another position upon postural change or head tilting to one side	Masquerade syndromes of malignancy, crystalline lenticular pseudohypopyon, pseudoendophthalmitis after IVTA

Table 1 "Naming-meshing" system for sediment formation in the dependent part of the eye (observational, behavioral, locational, and etiopathologic definition of precipitations' characteristics)[1-45] (continued)

Naming	Definitions-characteristics-frequency	Meshing (etiology)
8. Clinical behavior (scleral show) [1,3,4-10]		
Warm (pseudo)hypopyon	An acute type of perilimbal vascular injection with deep and superficial vessel dilations (a bloodshot eye) in the presence of severe anterior segment inflammation	OBD, HLA-B27-related AAU, pseudohypopyon from retinoblastoma
Cold (pseudo)hypopyon	Lack of periglobal injection despite the presence of severe intraocular inflammation (an uninjected white eye in a hot disease)	OBD, after IVTA injection (may be called cold pseudohypopyon), tumoral sediment, subacute neuroretinitis
9. Laterality-Alternation-Symmetry[1,4-6]		
Unilateral hypopyon	In about one-third of cases in the same eye at a given time	OBD, HLA-B27-related AAU
Alternating hypopyon	Interrupted occurrence with regular succession being interspersed with opposite involvement	Rifabutin-induced hypopyon uveitis, OBD, HLA-B27-related AAU
Non-alternating hypopyon	Regular unilateral involvement of the same eye	After IVTA injection
Bilateral hypopyon	Simultaneous or non-simultaneous (sequential) involvement of both eyes	Develops in more than half of the cases
Symmetrical hypopyon	Bilateral simultaneous hypopyon at the same time	Rifabutin-induced hypopyon uveitis
Non-symmetrical hypopyon	Non-simultaneous, successive, asymmetrical bilateral uveitis with iridocyclitis in one eye and hypopyon in the other	OBD, rifabutin-induced hypopyon uveitis
10. Height (select regularly one)[1,4-6,8-9]		
Millimeter (mm)	*e.g.*, 3 mm in height or 3 mm hypopyon	The usual form that is important for the follow-up
Proportion	*e.g.*, one-third of the anterior chamber	May be used
Percentage (%)	*e.g.*, occupying 30% of the anterior chamber	May be used
11. Location(s)-number[14,28,38-43]		
Hypopyon		
Corneal	Layered collection within the cornea	Keratitis from *Ochrobactrum anthropi*
Anterior	Macro-, micro-, or angle-hypopyon in the anterior chamber of the eye	The most common and classical form
Double	Suppurative sediment both in the anterior chamber and within a cavitating stromal corneal abscess	Severe keratitis from *Pseudomonas aeruginosa*
Subretinal (posterior)	Inferior exudative retinal detachment with acute inflammation in the subretinal space	Sympathetic ophthalmia, ARN, presumed tubercular sclerauveitis, fungal endophthalmitis
Pseudohypopyon (Masquerades)		
Anterior	Macro-, micro-, or angle-pseudohypopyon in the anterior chamber of the eye mimicking a hypopyon uveitis	Metastatic or primary intraocular tumoral sediments, after IVTA injection, cholesterolosis bulbi, ocular leprosy, crystalline lenticular material
Endo(capsular)	In the capsular bag after lens surgery detected by pupillary dilation as a white posterior capsular plaque with or without anterior hypopyon	Chronic endophthalmitis by *P. acnes*, *Corynebacterium* species, *Actinomyces* species, *S. hominis*, or fungi
Lacteocrumenasia	A milky white liquefied fluid accumulation in the capsular bag from the occlusion of the anterior capsulorhexis opening	Phacoanaphylactic endophthalmitis after capsular block syndrome
Preretinal	A yellow-white preretinal layered exudation	Syphilitic retinal vasculitis
Intraretinal	A shifting "egg-yolk-like" sediment between RPE and sensory retina	Best's vitelliform macular dystrophy
Subretinal	Abnormal accumulation of the lymphocytes	Prolymphocytic leukemia
12. Purulence[1,4-6,19,21-24]		
Inflammatory hypopyon	Sediment consisting of exudates, proteins, necrotic tissue debris, by-products, and PMNLs with or without microorganisms	HLA-B27-related AAU, OBD, endogenous metastatic endophthalmitis, after IVTA injection
Suppurative hypopyon	A purulent hypopyon causing pus formation from infective etiologies	Bacterial, fungal, or viral severe corneal infections
Non-suppurative hypopyon	A non-purulent hypopyon without pus formation, but still an inflammatory hypopyon	OBD, herpetic uveitis, uveitis after laser iridotomy or PRP
Non-inflammatory (pseudo)hypopyon	Malignant sediment consisting of tumoral cells without inflammation, though may rarely have an inflammatory component	Primary or metastatic intraocular neoplasms
13. Sterility[1,3-6,8-14,44-45]		
Sterile hypopyon	Non-infective inflammatory sediment that does not contain any microorganism	OBD, HLA-B27-related AAU, recurrent corneal erosions
Sterile pseudohypopyon	Non-infective, non-inflammatory sediment that does not contain any microorganism	Tumoral pseudohypopyon, after IVTA injection (may be mixed with sterile endophthalmitis)
Sterile endophthalmitis	An inflammation without microorganisms, representing a toxic reaction either to injected CS itself or its preservative or the solvent	After IVTA injection (may be mixed with a sterile pseudohypopyon)
Pseudoendophthalmitis	Pseudoinflammation where injected CS itself masquerades as inflammation, though consists of CS crystals migrating from the vitreous into the anterior chamber	After IVTA injection (may form sometimes a sterile pseudohypopyon), or secondary to chronic vitreous hemorrhage
Non-sterile hypopyon	Infective inflammatory sediment (endophthalmitis) containing microorganisms along with exudates, proteins, necrotic tissue debris, by-products, and PMNLs	Severe fungal keratitis, exogenous or endogenous metastatic infective endophthalmitis, after IVTA injection (may be mistaken as pseudoendophthalmitis or sterile endophthalmitis)
14. Recurrency[1,4-6]		
Relapsing hypopyon	Returning of hypopyon after a clearance period	Ocular Behçet patients, HLA-B27-related AAU
Unilateral recurrent	Relapsing in the same eye	OBD, TINU syndrome
Bilateral non-simultaneous	Relapsing in one eye at a time (alternating)	HLA-B27-related AAU, OBD, rifabutin-induced uveitis
Bilateral simultaneous	Relapsing in both eyes at the same time	HLA-B27-related AAU, OBD, rifabutin-induced uveitis
Non-relapsing (pseudo)hypopyon	Sediment with no relapse	After IVTA injection

Table 1 "Naming-meshing" system for sediment formation in the dependent part of the eye (observational, behavioral, locational, and etiopathologic definition of precipitations' characteristics)[1-45] (continued)

Naming	Definitions-characteristics-frequency	Meshing (etiology)
15. Onset[1,4-6]		
Acute uveitis (±hypopyon)	Sudden-onset inflammatory attack with a limited duration fewer than 3mo	HLA-B27-related AAU, OBD
Chronic uveitis (±hypopyon)	Indolent (insidious)-onset inflammation with a more protracted course over 3mo	OBD, TINU syndrome, JIA
16. Pathology[1,4-6]		
Non-granulomatous uveitis	Chronic inflammation with predominated lymphocytes and plasma cells	OBD, ocular leptospirosis, relapsing polychondritis, herpetic uveitis, TINU syndrome, lens-induced uveitis of phacotoxic uveitis
Granulomatous uveitis	Chronic inflammation with predominated and activated macrophages with the presence of epitheloid cells or multinucleated giant cells	Sarcoidosis, VKH syndrome, herpetic uveitis, ocular leprosy, lens-induced uveitis of phacoanaphylactic endophthalmitis
17. Course (duration)[1,4-6,44-45]		
Transient (hypopyon)	Self-limited that disappears spontaneously or after treatment by CSs within hours or days	OBD, after IVTA injection, HLA-B27-related AAU
Persistent (pseudohypopyon)	Chronic, lasting for a longer time with no or minimal, if any, response to CSs	Metastatic or primary intraocular tumoral sediments, crystalline lenticular collection

AAU: Acute anterior uveitis; ARN: Acute retinal necrosis; CS: Corticosteroid; HSV: Herpes simplex virus; IVTA: Intravitreal triamcinolone acetonide; JIA: Juvenile idiopathic arthritis; OBD: Ocular Behçet disease; PMNL: Polymorphonuclear leukocytes; PRP: Panretinal photocoagulation; RPE: Retinal pigment epithelium; TINU: Tubulointerstitial nephritis and uveitis; VKH: Vogt-Koyanagi-Harada; VZV: Varicella-Zoster virus. A standardized definition using as many descriptive terms as possible from the above-listed classification scheme between number 1 and 17 in a given patient is essential for the detailed and expressive understanding of sediment formation in investigative articles or case reports (*e.g.*, a 25-year-old male ocular Behçet patient with bilateral, alternating, non-infective, non-granulomatous, warm, 3-mm, mobile, white macrohypopyon in the anterior chamber of the eye recurred after cataract surgery and disappeared within hours by corticosteroid therapy). This kind of strict and extensive hypopyon description may be expressed by dividing it into 2 to 3 appropriate sentences as needed. "Hypopyon" alone should always indicate a "sediment" formation of inflammatory origin in the anterior chamber of the eye. Otherwise, a sediment of either non-inflammatory origin or of an unusual location other than the anterior chamber should always be named "pseudohypopyon" to avoid confusion among authors and publications. It should be remembered that a definition as "a 5-year-old female patient with right sterile 2-mm macrohypopyon" would not be sufficient as sterile hypopyon simultaneously may indicate the description of both a "malignant or tumoral (pseudo)hypopyon" of *e.g.*, "retinoblastoma" and "suppurative but sterile hypopyon" of infective-inflammatory origin. Therefore, a "sterile hypopyon" needs one or more expressive. But still, a tumoral "sterile pseudohypopyon" may have an inflammatory component due to necrotic uveal changes in some instances. It should also be remembered that a "white pseudohypopyon" from uveal involvement in a patient with metastatic or intraocular tumor will present naturally as a "cold pseudohypopyon". Hyperemic eye in a leukemic pseudohypopyon, on the other hand, presents clinically as "warm pseudohypopyon", indicating either sediment's inflammatory component or scleral involvement. Although the sediment in lacteocrumenasia is inflammatory in origin, it is accepted as pseudohypopyon because of its location other than the anterior chamber in the capsular bag.

Formation of Sediment The formation of hypopyon or pseudohypopyon may be spontaneous as a result of intraocular inflammation or intraocular tumors, respectively, or may be provoked by local trauma after intraocular surgery.

Visibility of Sediment "Macrohypopyon" or "macroscopic hypopyon" defines a sediment formation within the anterior chamber of the eye that is externally visible to the naked eye, usually layered inferiorly and horizontally at the 6 o'clock position in an upright posture (Figure 1A). In some cases, however, such a macrohypopyon may be seen on downgaze only. Whatever the cause, the level of such a "macrohypopyon" should therefore be recorded as percentages or proportions of the anterior chamber or, preferentially, be stated in millimeters during both the initial diagnosis and follow-up period[1,4].

In some instances, however, hypopyon in the anterior chamber cannot be seen externally to the naked eye (even in downgaze position) but is only visible on biomicroscopic examination and, therefore, is termed "microhypopyon" (Figure 1B). Furthermore, and clinically more importantly, some cases present with "occult hypopyon" that is neither visible to the naked eye externally nor on the slit-lamp. This is a subcategory of "microhypopyon" and may be visible in the dependent anterior chamber angle only by gonioscopic examination, so called "anglehypopyon" (Figure 1C, 1D)[1,4-5]. All the above-mentioned three categories that describe the visibility of the sediment in the anterior chamber may also be used accordingly for "pseudohypopyon", which will be discussed later. Therefore, the collections should be termed "macro-pseudohypopyon", "micro-pseudohypopyon", and "angle-pseudohypopyon"[1,3,5].

Mobility of Sediment The etiological content of the sediment in the anterior chamber of the eye affects its position and movement speed with which it settles back to its first position. A head-tilt test or a posture change of the patient may cause the dispersion of the collection or a total dislocation into another position within seconds or minutes when it contains lower or no concentration of fibrinous exudate as in "tumoral pseudohypopyon". This kind of (pseudo)hypopyon is termed "mobile or shifting (pseudo)hypopyon"[1,3-6].

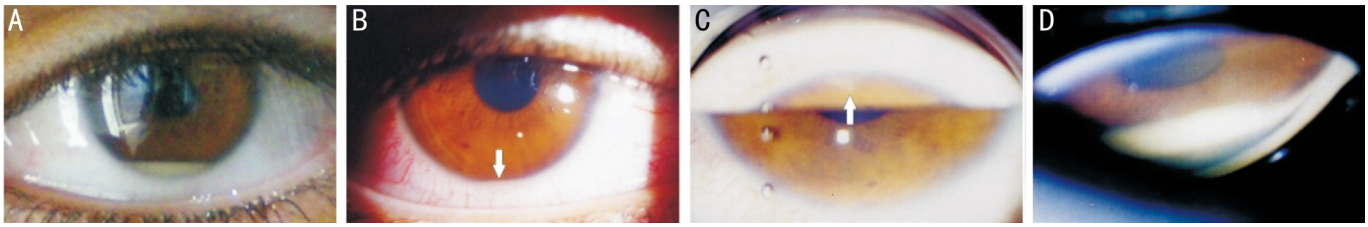

Figure 1 Definition of inflammatory sediment formation in the anterior chamber of the eye A: “Macrohypopyon” or “macroscopic hypopyon” is easily visible to the naked eye externally; B: “Microhypopyon” is not seen externally to the naked eye even in downgaze position, but is visible to the eye on biomicroscopic examination only (arrow); C and D: “Occult hypopyon” or “anglehypopyon” (arrow) is a subcategory of “microhypopyon”, which is neither visible to the naked eye externally nor on the slit-lamp with gonioscopic examination.

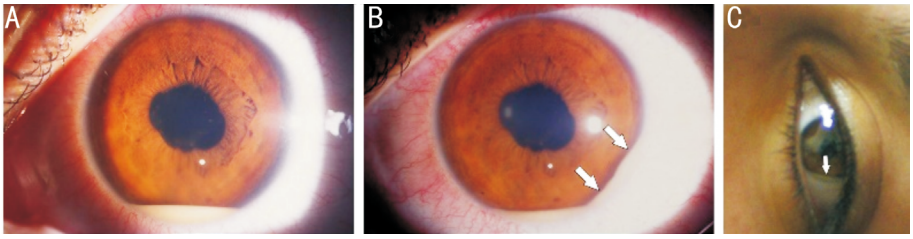

Figure 2 The characteristic of mobile hypopyon in ocular Behçet disease in the acute stage A layered hypopyon slowly shifts from its horizontal position (A) into the direction of head tilting within minutes (B, arrows) and completely dislocates into the lateral part of the eye upon permanent leaning to the left side (C, arrow).

Classically, infectious (microbial) endophthalmitis and non-infectious inflammation (*i.e.*, HLA-B27-related AAU) result in “immobile, non-shifting (plastic) hypopyon” that contains a high level of fibrinous exudates during the acute phase of inflammation[1,7]. In turn, “mobile or shifting hypopyon” in the anterior chamber is characterized by “aqueous flare” that consists of serous protein. The foremost pattern for “mobile hypopyon” is seen in OBD, which slowly shifts from its horizontal position (Figure 2A) into the direction of head tilting within minutes (Figure 2B) and completely dislocates into the lateral part of the eye upon permanent leaning to one side (Figure 2C). Another form of “shifting hypopyon” is culture negative “sterile endophthalmitis” after intravitreal injections of triamcinolone, which will be discussed later[1,3].

Pseudohypopyon in the eye has dispersive properties with head shake and gravitationally shifts or completely dislocates into another position upon permanent postural change or head tilting to one side. Such a collection is called “mobile” or “shifting pseudohypopyon”. The dislocation of the collection within seconds is a pathognomonic feature of “neoplastic pseudohypopyon”[8-9].

Clinical Behavior of Sediment The term “warm hypopyon” is used for the anterior chamber sediment of inflammatory origin that is clinically associated with an acute type of global redness (Figure 3A), as generally expected, along with conjunctival, episcleral, and deep scleral vasodilatations, which usually develop over a period of hours (sudden onset) or days, presenting as periglobal circum-corneal (perilimbal) dusky red hyperemia with a violaceous hue (ciliary injection or flush) where the ciliary and scleroconjunctival circulations anastomose (Figure 3B)[6-7]. In advanced cases, a “blood-shot eye” is seen, for instance, in HLA-B27-related AAU (Figure 3C). However, there may be an intriguing discrepancy between the severity of intraocular inflammation (hypopyon) and the status of periglobal injection (white or uninjected eye in a “hot disease”) that presents atypically and, therefore, is called “cold hypopyon” (Figure 3D)[1]. In other words, the eye may externally be so quiet that it may mask the underlying severe uveitis with hypopyon formation. Indeed, this kind of surprising disparity may be observed in OBD as a pathognomonic finding (Figure 3D)[1]. Furthermore, there may also be a negative correlation between the degree of hypopyon formation in the anterior chamber and the status of posterior segment involvement. That is, a severe hypopyon may be encountered in an uninjected white eye with good visual acuity.

In light of the explanations stated above for “cold” and “warm” hypopyon regarding the scleral show, an opposite approach or nomenclature is used for pseudohypopyon. Because “neoplastic masquerade syndromes” are non-inflammatory in nature, a “tumoral pseudohypopyon” demonstrates a “cold scleral show” that presents with an “uninjected white eye” (without pericorneal ciliary injection) as usually expected[1,8-9]. On the other hand, uveal irritation of tumoral cells may cause an atypical presentation, resulting in unexpected inflammatory injection (red eye), called “tumoral pseudohypopyon” with a “warm scleral show”[8]. In other words, the eye may externally be so red that the neoplastic collection may mimic

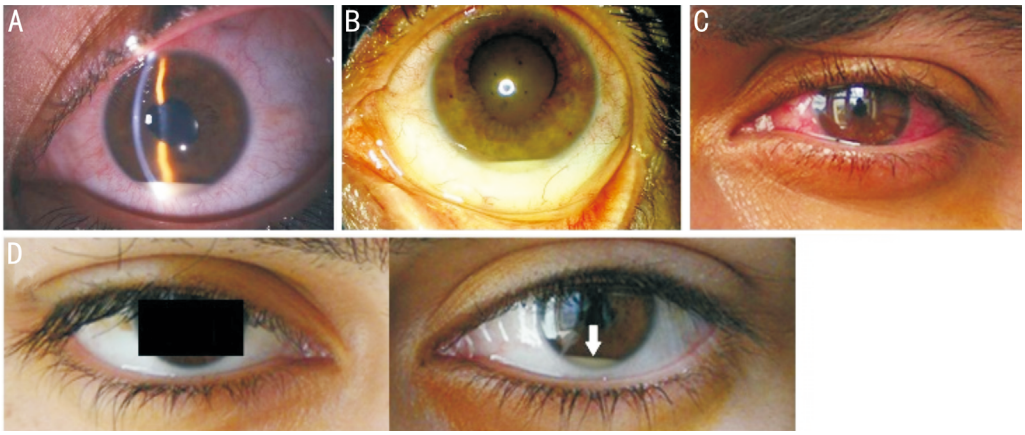

Figure 3 Definitions for "warm" and "cold" hypopyon A-C: "Warm hypopyon" is used for the anterior chamber sediment of inflammatory origin that is clinically associated with moderate (A), mild (B), or acute type of global or perilimbal redness (C), which defines a "blood-shot eye". D: "Cold hypopyon" in the left eye (arrow) in a patient with ocular Behçet disease that represents the discrepancies between the severity of intraocular inflammation (hypopyon) and the status of periglobal injection ("white" or "uninjected" left eye in a "hot disease"; please compare the scleral whiteness of the left eye with hypopyon uveitis with that of the uninvolved right eye of the same patient. They are similar in appearance).

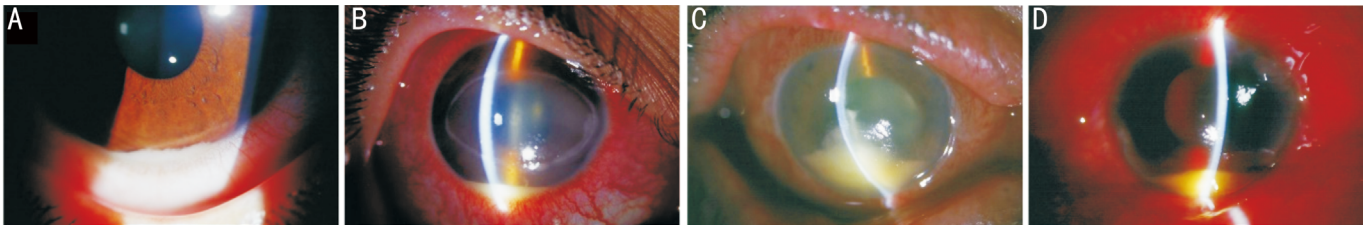

Figure 4 Distinctive clinical characteristics between hypopyon and pseudohypopyon using slit-lamp photographs A: An anterior chamber lumpy (wavy) sediment from retinoblastoma that is layered as "convex (peripherally heaped up) white pseudohypopyon" in a white eye (cold pseudohypopyon); B: "Horizontally layered white hypopyon" from long-term contact lens use showing moderate conjunctival hyperemia and ciliary injection; C: "Triangular hypopyon" is encountered in severe microbial keratitis that is characterized by centrally "heaped up" sediment rather than at its edges, showing marked conjunctival hyperemia, fibrinous exudation, and posterior synechia; D: "Yellow, centrally heaped up hypopyon" in a patient with panophthalmitis, showing chemosis and marked conjunctival hyperemia.

an inflammatory "hypopyon" and, therefore, can mask the underlying tumoral nature of the precipitation[9]. Indeed, this kind of surprising discrepancy can be observed due to sediment formation in the anterior chamber from retinoblastoma, which may sometimes be layered differently, as "convex pseudohypopyon" with a lumpy or wavy appearance (Figure 4A)[1,3,8-9]. Obviously, if such neoplastic anterior chamber sediments are visible to the naked eye in a white eye, "a cold tumoral macro-pseudohypopyon" would be preferred to fully express the descriptive characteristics of the collection.

Apart from tumoral sediment formation itself, a "non-tumoral pseudohypopyon" consisting of cholesterol crystals in the anterior chamber may be observed in eyes with advanced cases of cholesterolosis bulbi with or without subretinal crystals upon vitreous hemorrhage after severe trauma, long-standing retinal detachment, and retinoblastoma[10].

Sterility of Sediment "Sterile hypopyon" is defined when the sediment contains no microbial organism. OBD and HLA-B27-related AAU are two common examples of "sterile hypopyon"[1,6]. Pseudohypopyon is also a sterile collection since it originates from non-infective non-inflammatory anterior chamber collections of neoplastic etiologies of masquerading syndromes[8-9]. Likewise, endotoxin-triggered hypopyon by instrument cleaners, residual polishing compound that appears on the intraocular lens (IOL) surface, and post-intravitreal triamcinolone acetonide (IVTA) injection pseudoendophthalmitis are some examples of sterile hypopyon[11]. One of our cases demonstrated that a mobile and white sterile "crystalline pseudohypopyon" might present as a layer of snowdrift deposits in the anterior chamber of the eye that settled down inferiorly and was associated with freely floating crystals in the aqueous humor, resembling a "snowy Christmas Eve" appearance as a result of spontaneous central openings on the anterior lens capsule with lens absorption[3]. Topiramate-induced bilateral sterile hypopyon uveitis has also been reported[12].

Toxic anterior segment syndrome (TASS) is a form of acute, sterile inflammatory reaction in the anterior chamber of the eye

after intraocular surgery and characteristically presents within the first day due to denatured ophthalmic devices or lenses and causes hypopyon formation in up to one-fifth of cases[13]. Intraocular pressure is significantly increased with painless decreased vision, conjunctival injection, corneal edema, anterior chamber cells, flare, and fibrin[14]. The differential diagnosis between non-infectious sterile inflammation (*i.e.*, TASS) and infectious endophthalmitis is vital for rapid and appropriate management to prevent sight-threatening complications.

"Suppurative hypopyon" defines a "purulent hypopyon", which results in the development of pus formation and is caused by infective etiologies[1,4]. It depends on the strength of the local chemotaxic stimuli with activation of the alternative complement pathway and tissue destruction. Such a hypopyon formation with its clinical consequences is also known as "infective (non-sterile) inflammatory hypopyon"[5]. It should be remembered that hypopyon is a marker of severe inflammation in such cases that often leads to the development of inferior peripheral anterior synechia formation, if not treated effectively and aggressively[1,6]. However, a "suppurative hypopyon" may also present as "sterile inflammatory hypopyon", if the sediment has no microbial agent, which is seen in some non-penetrating bacterial corneal infections[4-6]. "Non-suppurative hypopyon", in turn, describes a non-purulent hypopyon formation that does not result in pus formation, though it is still an inflammatory precipitation[1].

Recurrency of Sediment Hypopyon is termed "recurrent" or "relapsing" if there are two or more episodes of ocular inflammation separated by a disease-free period with complete resolution of a previous acute flare[1]. The recurrence may be unilateral (in the same eye every time), bilateral simultaneous (in both eyes), or bilateral non-simultaneous (alternating), relapsing in one eye at a time. OBD and HLA-B27-related AAU are the most common forms of relapsing uveitis[1,4-6].

Color of Sediment Numerous exogenous infectious diseases are associated with hypopyon formation, including toxocariasis, syphilis, tuberculosis, and other specific agents[6]. Endogenous endophthalmitis may also cause hypopyon due to hematogenous spread of bacterial or fungal microbials from distal localization into the eye[4-6]. The symptoms and signs are similar to exogenous endophthalmitis. The color of the sediment may suggest a specific etiology in some cases. Although "white" or "grayish-white hypopyon" (Figure 3A, 3B, 3D) or "pseudohypopyon" (Figure 4A) is encountered in almost all cases[1,8-9], "yellow hypopyon" in the presence of red blood cells in panophthalmitis (Figure 4D) or "pink-colored hypopyon" in the absence of erythrocytes or hyphemia may be observed in *Serratia marcescens*-precipitated endophthalmitis that produces a red pigment[15]. "Pink hypopyon" due to Klebsiella pneumonia or ocular toxocariasis has also been reported[16]. Moreover, "darkly pigmented hypopyon" after tuberculosis[17] or "black-colored pseudohypopyon" can be seen in some primary intraocular or metastatic necrotic uveal melanomas[18] whereas progressively darkening "pigmented hypopyon" from tan to black in color is observed in *Listeria monocytogenes*- and *Serratia marcescens*-induced endogenous endophthalmitis as a result of melanin pigment dispersion into the anterior chamber from necrotic iris, leading to the hypopyon's dark hue[19-21]. Rarely, spontaneous hyphema may result in a "blood-tinged", "blood-streaked", "blood-stained", or "hemorrhagic" pseudohypopyon as a presenting feature of leukemia, lymphoma or AIDS[8-9,22-25]. Herpetic keratouveitis as a result of severe *Herpes Simplex* virus or *Varicella Zoster* virus may also cause anterior chamber hypopyon with or without hyphemia and endothelium folds, regardless of the presence of polymicrobial superinfection, realizing a pattern called "candy-cane hypopyon"[24]. A sterile "brown pseudohypopyon" may also be encountered as a result of hemolytic "erythrocyte ghost cells" glaucoma[26].

Shape, Number, Orientation, and Position of Sediment Although the clinical appearance of hypopyon is identical for infective and non-infective diseases, which are generally layered horizontally (Figure 4B)[1], hypopyon associated with, for instance, severe microbial (bacterial) keratitis is typically curved centrally rather than at its edges and, therefore, is triangular in appearance rather than flat (heaped-up triangular hypopyon; Figure 4C). In addition, chemosis, marked conjunctival hyperemia, fibrinous exudation, and posterior synechia are encountered in such cases (Figure 4C, 4D)[1,4]. The typical form of "pyramidal-shaped hypopyon" with unsharp borders, if it is associated with prominent geographical corneal infiltration and satellites, strongly suggests the diagnosis of fungal keratitis[1,6].

"Ring hypopyon" has been described for a patient with meningococcal endophthalmitis[27] and "double hypopyon" has been reported for the pus that is visible both in the anterior chamber and within a cavitating corneal abscess in the mid to deep stromal layers secondary to severe keratitis[28]. "Oblique" or "vertical hypopyon" was reported for a bedridden patient who was lying on his left side with no voluntary head turn due to chronic immobility caused by a previous stroke[29]. Anecdotally, a non-infective "pseudohypopyon" has also been reported secondary to intravitreal injection of dexamethasone implants as well as in chronic vitreous hemorrhage or vitrectomy that was stated to have the appearance of precipitation of muddy sand[30-31]. Similarly, a "white or whitish-red pseudohypopyon" has been described for the fluid resembling a hypopyon that filled the space created by localized bullous separation of Descemet's membrane after years of cataract surgery[32].

In the posterior segment, an "egg-yolk-like sediment" in the manner of a pseudohypopyon-like picture from material located intraretinally between the retinal pigment epithelium and the sensory retina is a well-known characteristic of Best's vitelliform macular dystrophy or degeneration that may shift slightly with head turning to the side[33]. Posterior "boat/crescent-shaped hypopyon" in fungal endogenous endophthalmitis has recently been reported in one case[34].

"Inverse hypopyon" is used for anterior chamber exudates that are positioned superiorly at the 12 o'clock position, which may be encountered with infectious scleritis[35]. Similarly, "reverse" or "inverted pseudohypopyon" may be seen among post-vitrectomy patients as a result of emulsification of silicone oil tamponade, which is located superiorly in the anterior chamber of the eye since silicone is lighter than the aqueous humor[36-37].

Anatomic Localization of Sediment Although the term "hypopyon" traditionally implicates the collection of the sediment in the anterior chamber of the eye, corneal, (endo)capsular, and posterior locations may also be encountered[38-39]. Similarly, the term pseudohypopyon, when used alone like hypopyon, defines the precipitation in the anterior chamber of the eye, though a wide range of sediment formation may occur in any part of the eye including corneal, endocapsular, preretinal, intraretinal, and subretinal locations[40-41].

"Capsular" or "endocapsular (pseudo)hypopyon" is used to describe sequestered material in the capsular sac between the IOL and the posterior lens capsule. Relapsing, low-grade, chronic and delayed inflammation may be encountered within weeks following ocular surgery, resulting mostly from indolent organisms such as coagulase-negative *Staphylococcus*, *Propionibacterium acnes* endophthalmitis, *Corynebacterium species*, or *Actinomyces species*, and one-third of cases have anterior chamber hypopyon[14,42]. This can be detected only after pupillary dilation with a white posterior capsular plaque, sometimes known as "toxic lens syndrome" that was used originally to denote a sterile postoperative inflammation after IOL implantation, though the inflammation often has nothing to do with the IOL[38]. Anecdotally, capsulorhexis-related late postoperative lacteocrumenasia defines a benign milky-white accumulation of a liquefied substance within a capsular bag between the posterior surface of implanted IOL and the anterior surface of the distended posterior capsular bag, formed because of the occlusion of the anterior capsulorhexis opening[43].

DISCUSSION

Various studies including ours[44-47] have indicated that single or repeated IVTA (a relatively insoluble long-acting depot steroid with 18.6d half-life) injections, which have been used increasingly for the treatment of various ocular diseases in clinical practice, may present as three ophthalmic forms; 1) a "transient rapidly-shifting pseudohypopyon" masquerading as a "pseudoendophthalmitis" (a non-infectious, non-inflammatory "sterile sediment") with no conjunctival congestion; 2) a culture negative "sterile endophthalmitis" (without any infectious microorganisms) with mild inflammation, mild conjunctival congestion, mild vitritis, and painless eye with the absence of lid edema, probably as a result of a toxic reaction to corticosteroids (CSs) itself or its preservative (*e.g.*, benzyl alcohol), the solvent agent or the inadequate osmolarity of the vehicles alone, especially in patients with a prior ocular history of uveitis. Head-tilt test shows the shifting nature of the hypopyon, which resolves spontaneously; and finally 3) a post-intravitreal injection "infectious endophthalmitis" (non-sterile, culture positive hypopyon) in phakic, aphakic or pseudophakic patients with severe vision loss, pain, marked conjunctival congestion, redness, mild corneal edema, prominent vitritis, and fibrinoid hypopyon formation in three-fourth of cases (Figure 4C, 4D). Taken together, signs of infectious or non-infectious endophthalmitis including non-crystalline hypopyon may not be observed if the solvent agent is removed by filtration or when preservative-free triamcinolone is used. Indeed, non-infectious endophthalmitis is encountered more commonly with triamcinolone containing preservative when compared with preservative-free IVTA injections[44].

Although post-injection transient pseudohypopyon may look like inflammation or even endophthalmitis, such a "steroid pseudohypopyon" actually consists of white deposits of injected triamcinolone crystals[44]. They partially migrate from the vitreous cavity into the anterior chamber of the eye and settle down inferiorly within hours, especially when the injection is not performed to the center of the vitreous, though the incidence is less than 1%[44-45]. However, factors indicating sterile rather than infectious endophthalmitis include earlier presentation within one to three days of injection, lack of pain or aqueous cells in a white (cold) eye (pseudohypopyon) along with relatively rapid recovery of vision that clears spontaneously within 2 to 4d without corneal or trabecular complication. Such a collection was reported for a pseudophakic patient with anterior chamber IOL implantation lacking a capsular barrier, allowing open communication between the vitreous cavity and the anterior chamber[47].

The distinction of "pseudohypopyon" from "hypopyon" and the differentiation of "infectious" from "non-infectious sterile" inflammation is of utmost importance for an ophthalmologist since their treatments and prognoses are entirely different[8-9,48-52]. The crystalline structure of the sediment from triamcinolone acetonide can easily be identified using high magnification slit-lamp biomicroscopy[44]. In some cases, crystal deposits may be seen as adherent to the endothelial surface. On the other

hand, it should be kept in mind that a high level of intravitreal steroid may mask typical symptoms or manifestations of infection-related non-sterile intraocular inflammation, though post-injection sterile inflammation or pseudoendophthalmitis may still be encountered due to the toxic solvent agent of triamcinolone acetonide, as stated above. Therefore, patients with no capsular barrier who present with pseudohypopyon or hypopyon immediately after IVTA injection should be observed closely for a few days for possible resolution prior to being treated for endophthalmitis.

Appropriate Description of Sediment in Articles The type of sediment for a given patient should be named as descriptive as possible using the first column of the novel classification system in Table 1; *e.g*., "a 25 year-old female patient with unilateral (right), warm, horizontal, non-shifting, 3-mm white macrohypopyon in the anterior chamber of the eye that disappeared within 3d after anti-inflammatory therapy" and then be matched to a potential list of etiologies (*e.g*., HLA-B27-related AAU)[1,4-6]. Afterwards, targeted questioning with selected medical and/or specific laboratory investigations based on the prepared shortlist will then identify a probable etiology and type of hypopyon or pseudohypopyon[1,8-9]. By thorough clinical ocular and systemic history with the appropriate selection and interpretation of straightforward investigations, it is usually now possible for the ophthalmologist to make or exclude a systemic diagnosis, predict the ocular prognosis, and direct selected patients to the proper physician.

Sex, Frequency, and Course of Hypopyon HLA-B27 related AAU and OBD are the most common causes of hypopyon formation[1,4-5]. If such a unique clinical finding is diagnosed and treated promptly and properly, sight-threatening complications can be prevented. Hypopyon from any cause occurs more frequently in men than in women and it is bilateral in more than two-thirds of cases[1]. Taken together, the incidence of hypopyon formation occurs in about one-tenth of patients with all kinds of uveitis[1,4-5]. However, the most common prototypes of relapsing explosive uveitis with a tendency to cause hypopyon were found to be HLA-B27-related AAU and OBD, followed by fungal endophthalmitis[34-50]. Taken on an individual basis, one-fourth to one-third of ocular Behçet patients and up to one-half of patients with HLA-B27-related iridocyclitis experience hypopyon uveitis during the disease course, especially in untreated patients[1,4-5]. However, the frequency of recurrent hypopyon formation has been found to be much higher in OBD (more than three-fifths of eyes) than in HLA-B27-associated uveitis (about one-eighth of eyes)[1,4-6].

The prevalence or frequency of hypopyon is much higher than reported or known among various clinical series in the literature for both OBD and other uveitis because many articles that have indicated the incidence of hypopyon did not report that the anterior chamber angle was evaluated to search whether there was an "occult hypopyon", which may easily be missed by the ophthalmologist if diagnostic criteria are not followed strictly in searching for this unique clinical manifestation.

A large study has demonstrated that eyes with or without hypopyon have a similar incidence of band keratopathy, posterior synechia, ocular hypertension, hypotony, macular edema, epiretinal membrane, and cataract or glaucoma[5]. In addition, post-hypopyon eyes were more likely to gain 3 lines of vision and were less likely to develop 20/200 or worse visual acuity when compared with eyes not developing hypopyon. Similarly, more severe inflammation, hypopyon formation and higher recurrence rate of anterior uveitis have been observed in the HLA-B27 positive group when compared with the HLA-B27 negative group, though no significant differences have been encountered for final ocular and visual outcomes between these two groups with rather favorable prognosis in HLA-B27-associated AAU[53-54].

Although the visual prognosis for patients with hypopyon uveitis is generally good when compared with other forms of uveitis, it is still a cause of disability when flares are frequent and the final visual acuity is poor, especially in OBD, which indicates the significance of its distinction from other ocular or non-ocular systemic diseases that cause hypopyon formation in the anterior chamber. Indeed, the visual acuity for the first episode of hypopyon formation from any cause was found to be worse than 0.1 in two-thirds of eyes, whereas the final visual acuity was worse than 0.1 in about one-half of eyes, nine-tenths of which were from OBD[55]. Fluorescein angiography was stated to be an important investigation for predicting poor visual outcome[56].

Hypopyon occurs in three-fourths of infective endophthalmitis, a large hypopyon indicates poor prognosis[4], and hypopyon occurring following cataract surgery should be accepted as infectious till proven otherwise.

Evaluation of Patients with Hypopyon and Pseudohypopyon A detailed ocular and systemic anamnesis including demographic data and geographic history should be obtained first. Distinctive bilateral ophthalmic evaluation is essential to guide the differential diagnosis of hypopyon and pseudohypopyon. Former attacks, history of ocular trauma, intravitreal injection or surgery, systemic disorders, immune status, previous medical treatments and the status of response, and family history should all be obtained. Similarly, external evaluation may reveal corneal ulcer, keratitis, scleritis, very fine (dusty) keratic precipitates, iris changes, abnormal intraocular pressure, and intravitreal inflammatory cells. Corneal confocal microscopy, laser flare photometry, optical coherence tomography, fluorescein angiography, and

ultrasonography may be used for directing the treatment of patients with a hypopyon. The anterior chamber or vitreous tap may be necessary for the detection of microbial agents[1,4-6].

Hypopyon uveitis presents clinically with gradual blurred or decreased vision, sudden onset and progressive periorbital or global pain with a reduction in accommodation, changed periglobal blood flow and vessel permeability, red eye characterized by perilimbal hyperemia and deep ciliary injection showing abrupt vasodilatation in the conjunctival, episcleral, and scleral vessels with chronic floaters, reactive miosis, photophobia, and lacrimation that may develop over several days. The pupil may appear sluggish but is better defined as small and irregular. In addition, pain and photophobia may precede biomicroscopic findings due to unobserved ciliary body inflammation. Given that hypopyon comes in bursts and typically affects young adults in their most productive ages, an ophthalmologist must be familiar with the full spectrum of the sediment's presentations[1].

In conclusion, hypopyon and pseudohypopyon signify a sedimentation in the eye and may be triggered respectively by inflammatory or tumoral conditions. Therefore, the distinction of "pseudohypopyon" from "hypopyon", which may be "infectious" or "non-infectious", is vital for an ophthalmologist for early diagnosis, as the management and prognosis are completely different. For this reason, a detailed anamnesis, stepwise systemic examination, and detailed evaluation of the sediment's characteristics are cornerstones for identifying the possible etiology, directing the patient, and initiating immediate and proper treatment, which can be made using the introduced up-to-date naming-meshing system. Keratitis and exogenous or endogenous endophthalmitis are the most frequent etiologies of infectious hypopyon and are associated with an increased risk of profound damage and vision loss, whereas OBD and HLA-B27-related AAU are the most common reasons for non-infectious hypopyon uveitis with lower risk of sight-threatening complications. On the other hand, the most common causes of tumoral pseudohypopyon include leukemia, vitreoretinal lymphoma, and retinoblastoma. It should be kept in mind that the knowledge obtained from a thorough examination in systemic diseases may be related to the ophthalmic involvement in a specific disease.

ACKNOWLEDGEMENTS

Conflicts of Interest: Evereklioglu C, None; **Sener H,** None; **Sonmez HK,** None; **Polat OA,** None; **Gulmez Sevim D,** None; **Arda H,** None; **Horozoglu F,** None.

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