Fungal Endophthalmitis

Alessandro Invernizzi

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Introduction

Endophthalmitis is defined as the intraocular presence of infectious microorganisms (bacteria or fungi), involving the vitreous and/or the aqueous humors, accompanied by a variable degree of inflammatory reaction.

Endophathalmitis can be exogenous, when the infectious agents penetrate the bulb from outside the body (following eye surgery or trauma), or endogenous when it occur as a result of hematogenous spread of microorganisms into the eye.

The epidemiology of fungal endophthalmitis is highly influenced by the environment, the climate, and people living conditions. In developed countries, where eye surgery is performed with highly standardized aseptic procedures, fungal endophthalmitis are mainly endogenous, usually related to prolonged hospitalization, indwelling catheters, or immunosuppressive treatments. On the contrary, in hot-climates developing countries, traumatic wounds are frequent and eye surgery, as well as after care, are often characterized by poor quality control measures, especially in rural settings, making exogenous endophthalmitis the more frequent cause of fungal intraocular infectious in these areas.

Although several agents have been demonstrated in fungal endophthalmitis and the prevalence of single species can widely vary among different climatic areas, endogenous endophthalmitis are predominantly caused by yeasts (*candida* spp), whereas exogenous infectious are mainly sustained by molds (*aspergiulls* spp.). Symptoms and clinical features widely vary depending on the causing agent and the infectious location within the eye, ranging from an indolent low grade inflammation to a devastating necrotizing process.

Endogenous invasion of the eye usually begins with the localization of microorganisms carried by the bloodstream at the level of the choroid or, more rarely, the retina (fungal chorioretinitis). At this time, symptoms are usually mild, but can range from a severe vision loss when posterior pole is involved to a completely silent condition, in case of peripheral lesions alone. As the fungi penetrate the eye structures and get into the vitreous, the inflammatory reaction increases and multiple whitish fluffy balls (typically disposed in a string of pearls fashion) can be detected, floating in the posterior chamber (Fig. 1). These aggregates are formed by a mixture of white cells and infectious microorganisms and represent the most characteristic sign of fungal endophthalmitis sustained by

A. Invernizzi (✉)
Uveitis and Ocular Infectious Diseases Service - Eye Clinic, Department of Biomedical and Clinical Science, Luigi Sacco Hospital, University of Milan, Milan, Italy
e-mail: alessandro.invernizzi@gmail.com; alessandro.invernizzi@unimi.it

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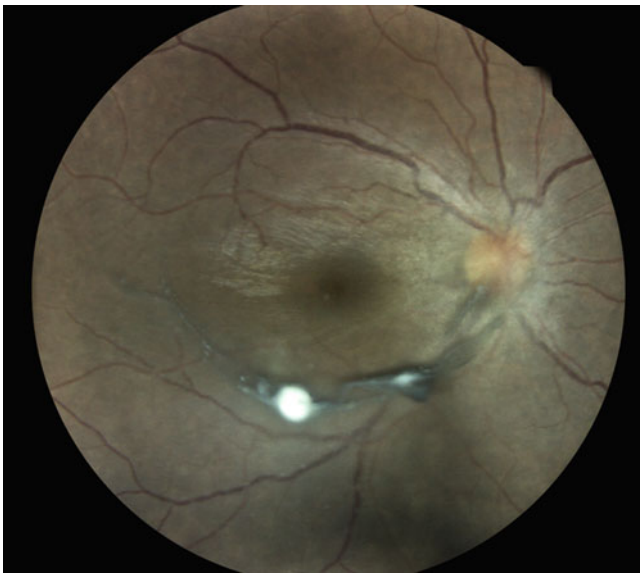

Fig. 1 Whitish fluffy vitreal aggregates in a patient affected by endogenous fungal endophthalmitis

candida spp. On the contrary, Aspergillus grows preferentially along subretinal pigment epithelium and subretinal space and the resulting clinical picture is characterized by large areas of retinitis or chorioretinitis. At this stage a severe vitreous haze can be present, along with anterior chamber reaction (acqueous cells, hypopyon, synechiae), leading to decreased vision, miodesopsias, and pain.

Post-surgical fungal endophthalmitis usually show a delayed onset and a less aggressive behavior as compared to bacterial, thus they should be suspected in case of indolent post surgical chronic uveitis. An exception is represented by *Aspergillus* spp., the most frequently isolated agents in post traumatic fungal endophthalmitis, which often show a rapid progression that may lead to early onset endophthalmitis and presentation similarly to bacterial endophthalmitis. The use of imaging investigations does not result really helpful in the diagnosis of fungal endophthalmitis for the laking of pathognomonic signs. Nevertheless optical coherence tomography (OCT) can be used while monitoring the disease progression as well as the alterations induced from the inflammatory and healing process in the retinal tissue. In addition, fluorescein angiography (FA) is useful to assess the possible presence of choroidal neovascularization as well as fibrovascular epiretinal membranes that can occur as a consequence of the prolonged inflammatory stimulus. The diagnosis of fungal endophthalmitis is hence mainly based on clinical findings and should be suspected every time a patient presents with intraocular inflammation associated with a known risk factor (Table 1).

Extra ocular findings interpretation is difficult during the diagnostic process. For example the presence of fungemia is not necessarily related to ocular infection as well as endophthalmitis can occur along with negative blood coltures. Intraocular demonstration of the fungal agent is hence the only technique that allows to confirm the presumptive clinical diagnosis. To reach this target, vitrectomy is the preferable procedure since it allows to collect samples, remove a large amount of microorganisms from the posterior chamber and deliver antifungal agents into the infected eye. On the contrary, aqueous taps has showed a low sensitivity in detecting fungal microorganisms. Once collected, the specimens can be analyzed by direct slides observations, culture or PCR assays. The treatment of fungal endophthalmitis is based on a combination of systemically and intravitreally administered antimycotic drugs (amphotericin B, triazole compounds) associated with pars plana vitrectomy in more severe cases. The visual outcome is variable ad depends on a correct management of the disease as well as on the lesions location, the causative agent and the stage at presentation.

Table 1 Risk factors for fungal endophthalmitis

Risk factors for fungal endophthalmitis	
Endogenous	Exogenous
Immunosuppression (iatrogenic) Prolonged hospitalization Indwelling catheters Diabetes Overuse of Antibiotics Hyperalimentation Neutropenia Acquired Immunodeficiency Syndrome (AIDS) Recent intra-abdominal surgery Intravenous Drug Abuse	Ocular traumatic wound Eye surgery Retained intraocular foreign body Wood/vegetables/soil debris penetrating the eye

Case 1: Vitrectomy is the Key

A 55 years old patient was referred to our unit for decreased vision in his right eye from the abdominal surgery department. He had underwent surgical asportation of a gastric cancer 1 month earlier and since then he was on parenteral nutrition. Blood tests revealed a mild neutropenia. Blood cultures for fungi or bacteria were negative.

At first observation, best correct visual acuity (BCVA) was hand motion in the right eye and 20/20 in the left. Right eye slit-lamp examination revealed anterior chamber severe inflammation, posterior synechiae and lens opacities. The fundus was not clearly visible because of an intense vitritis. Despite this a yellowish large lesion involving the whole posterior pole could be appreciated, left eye anterior segment and retina were within normal limits.

Considering the presence of multiple risk factors such as recent abdominal surgery and indwelling catheter, endogenous fungal endophthalmitis was immediately suspected. However bacterial etiology as well as a toxoplasmic

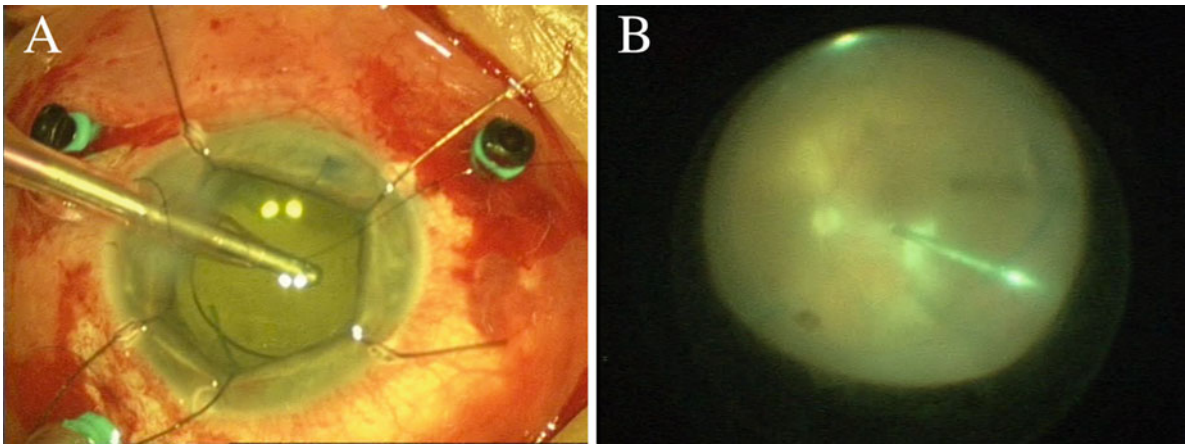

Fig. 2 (**a**) Because of the multiple posterior synechiae induced by the severe inflammation phacoemulsification and IOL implant needed iris mechanical retractors. Despite cataract extraction, fundus was barely visible due to the intense vitritis. (**b**) Collection of vitreous specimens from the pre retinal area just above the posterior pole lesion

retinochoroiditis reactivation could not be excluded. In such a sight treating condition, a prompt diagnosis and an early therapy onset are mandatory, thus vitrectomy was performed the same day.

After cataract removal and intraocular lens implant (Fig. 2a) some vitreous specimens were collected randomly through the posterior chamber and more posteriorly directly from the pre retinal space above the lesion (Fig. 2b).

Cultures and PCR require time thus some material was directly prepared for slices observation. Candida pseudohyphae were visualized at the microscope (Fig. 3) and real-time diagnosis of fungal endophthalmitis was made.

Surgery was hence completed with cleaning of the vitreous chamber and intravitreal amphotericin B injection. A systemic antimycotic therapy was also started. The endophthalmitis resolved in a couple of weeks and no other fungal lesions were detected in the patient's body. Unfortunately, the lesion healed with a scar in the macular region thus right eye BCVA at last examination was still poor (20/200).

This case demonstrates the key-role vitrectomy plays in the management of fungal endophthatlmitis, not only for posterior chamber cleaning but also for samples collection and diagnosis confirmation.

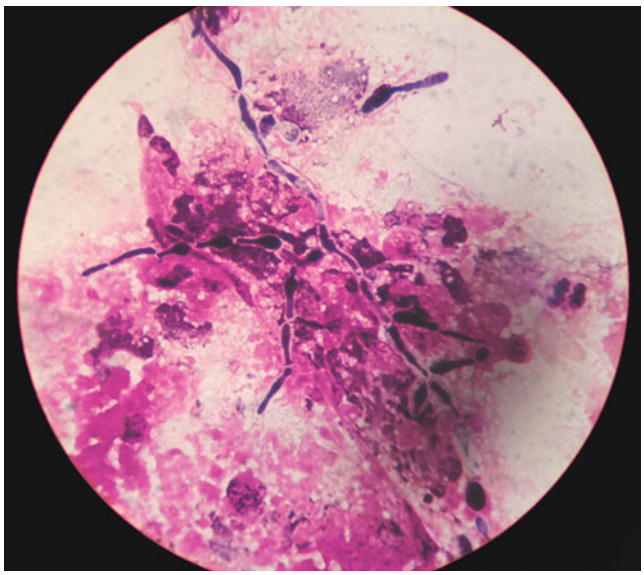

Fig. 3 Vitreous specimens slice analyzed by optical microscopy. Candida pseudohyphae are clearly visible between the vitreous debris

Case 2: Opportunistic Fungal Endophthalmitis should Rise the Suspect of HIV Infectious

A 33 years old man was visited during a screening program for homeless people. His visual acuity was good in both eyes. However, at fundus examination, multiple round-shaped small-yellowish lesions were visible (Fig. 4). No signs of intraocular inflammation were detectable.

In case of an intraocular spread of microorganisms, in absence of an inflammatory reaction, immunodeficiency should always be suspected. The patient was hence hospitalized for further investigations. Blood tests revealed the patient was affected by Acquired Immunodeficiency Syndrome (AIDS) complicated by a systemic criptoccosis. Specific treatments were started.

Fungal endophthalmitis can appear completely different in patients with a compromised immune system, the course can be faster while symptoms can be delayed for the lacking of vitreous inflammatory opacification. Moreover, some pathogens as *Criptococcus neoformans* are unable to infect immunocompetent hosts thus their identification is a landmark for immunodeficiency.

Case 3: Optical Coherence Tomography can Assess the Chorioretinal Lesions Regression and Confirm the Therapy Efficacy

A young diabetic patient complained of decreased vision in his left eye 2 weeks after abdominal surgery. At presentation his BCVA was 20/400 in the left eye and 20/20 in the right eye. At slit-lamp examination of left eye, anterior chamber showed a mild inflammatory reaction (cells ++), and anterior vitritis was detectable (Fig. 5a). Fundus examination revealed a yellowish lesion infiltrating the posterior pole and multiple fluffy vitreous aggregates (Fig. 5b).

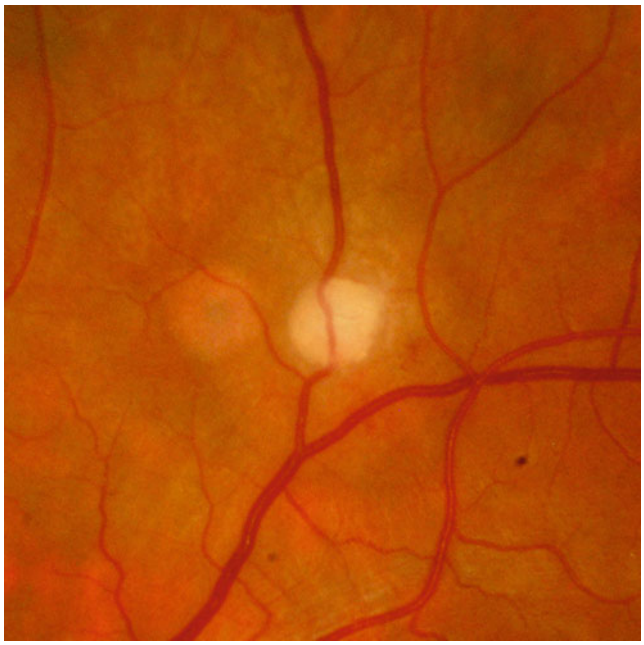

Fig. 4 Yellowish round-shaped lesion in a patient affected by Cryptococcus Neoformans. Note the absence of vitreous inflammatory reaction, suggestive for immunodeficiency

Optical coherence tomography allowed to assess the position and the extension of the lesion penetrating the retina and spreading into the vitreous. (Fig. 6a) Suspecting fungal endophthalmitis a systemic + intravitreal anti-fungal therapy was started. At 3 days from the therapy onset, anterior chamber inflammation worsened and hypopyon was detectable (Fig. 7). However, the OCT showed a clear regression of the chorioretinal lesion (Fig. 6b). On the base of these data, the anterior chamber worsening, firstly considered as a negative prognostic sign, was reinterpreted as a Jarisch-Herxheimer reaction, indicating treatment efficacy. Thus the antifungal therapy was continued and topical steroids were administrated.

Ten days later the anterior chamber was quite, the vitritis was resolving and the chorioretinal lesion was healed (Fig. 6c).

Case 4: Fungal Etiology Should Always be Suspected in Case of Late Onset Post-surgical Endophthalmitis

A 76 years old lady was referred to our center for decreased vision in her right eye since 2 weeks. She had undergone epiretinal membrane peeling 2 months earlier for a macular pucker and 1 month after surgery the eye was quiet. However at presentation she was still on topical steroids.

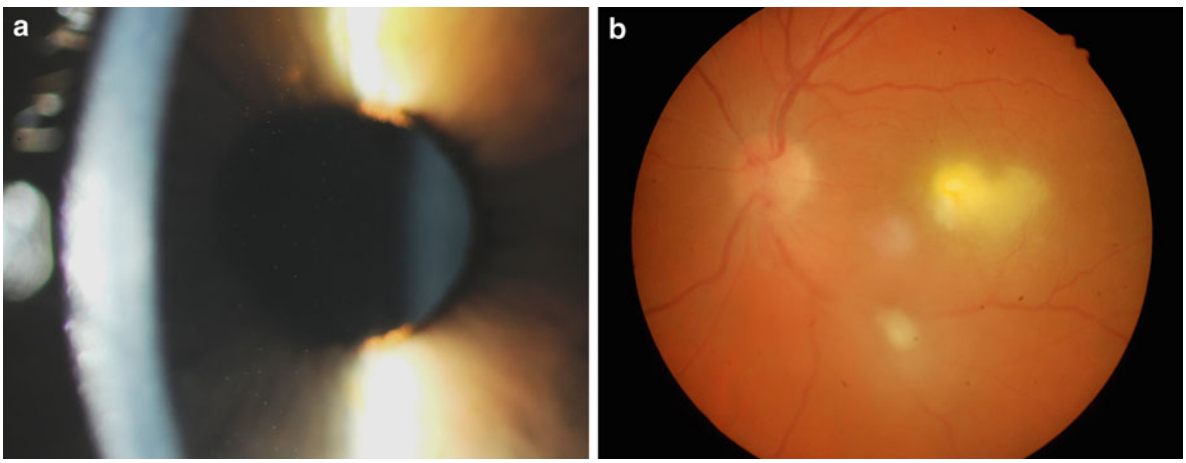

Fig. 5 (**a**) Anterior chamber mild reaction (cells ++). (**b**) A yellowish lesion infiltrating the posterior pole is visible at fundus examination along with Vitritis and fluffy vitreous aggregates

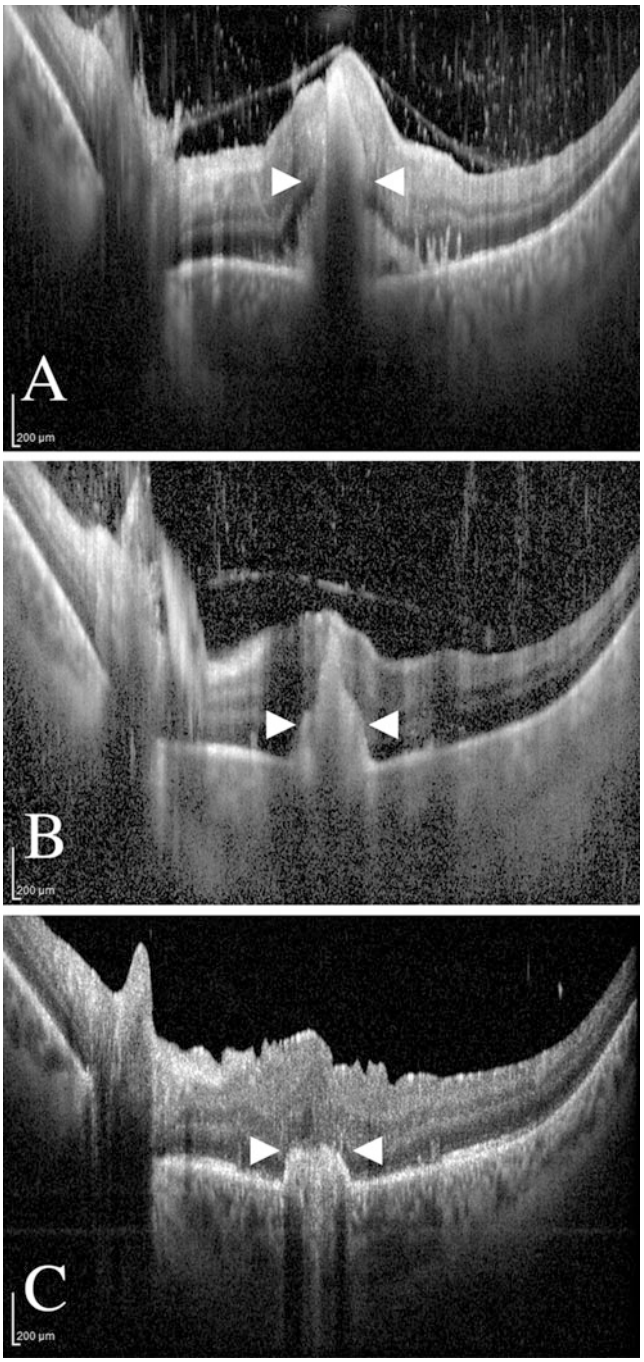

Fig. 6 (**a**) At presentation SD-OCT demonstrated a lesion located at the posterior pole involving the foveal region. The focus (*white harrowheads*) starts from the choroid, extends into the sub retinal space and, infiltrating the retina reaches, the vitreous cavity. (**b**) Three days after the therapy onset, despite the apparent worsening of the inflammatory reaction in the anterior chamber, the lesion is clearly regressing on OCT scans. (**c**) Ten days after OCT demonstrates healing of the infiltrating fucus and residual retinal layers alteration

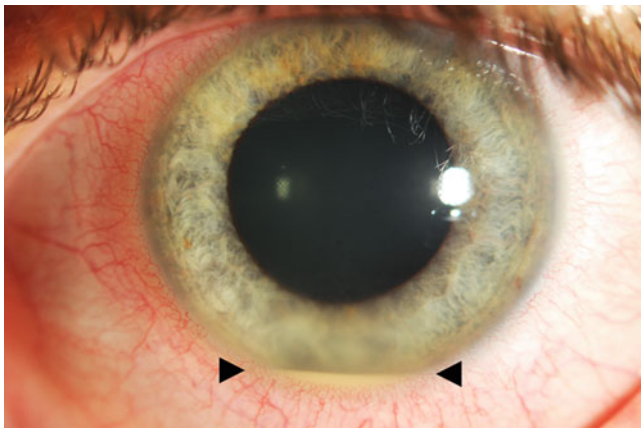

Fig. 7 Three days after the therapy onset anterior chamber presented an increased inflammatory reaction. Firstly considered as a negative prognostic sign, after the demonstration by OCT of lesion regression in the retina, the presence of hypopyon (*black arrowheads*) was reinterpreted as a Jarisch-Herxheimer reaction, indicating treatment efficacy

At slit-lamp examination, right eye showed a mild anterior chamber inflammation (cells ++), a fibrinous reaction on the IOL surface and a mild vitritis. The fundus didn't show significant alterations. Left eye was within normal limits.

Suspecting a late onset endophthalmitis, steroids were stopped and an antibiotic therapy with fortified antibiotics eyedrops was started. The day after the endophthalmitis worsened, hypopyon was visible at slit lamp examination (Fig. 8a) and multiple fluffy aggregates appeared in the vitreous (Fig. 8b).

Vitrectomy was performed and pan fungal PCR resulted positive for the presence of *fungal elements*. Intravitreal + systemic antifungal therapy was started with good response.

A delayed onset after surgery and a worsening after steroids drops discontinuation are both suggestive signs for fungal exogenous endophthalmitis.

Key Points

- Fungal endophthalmitis can be endogenous or exogenous.
- Symptoms and signs can widely vary according to the causative agent, the immune system status of the host, the lesions location, and the stage at presentation.
- The presence of intraocular inflammation associated with known risks factors should always rise the suspect for fungal endophthalmitis.
- Vitrectomy plays a main role in the diagnosis and management of these forms.

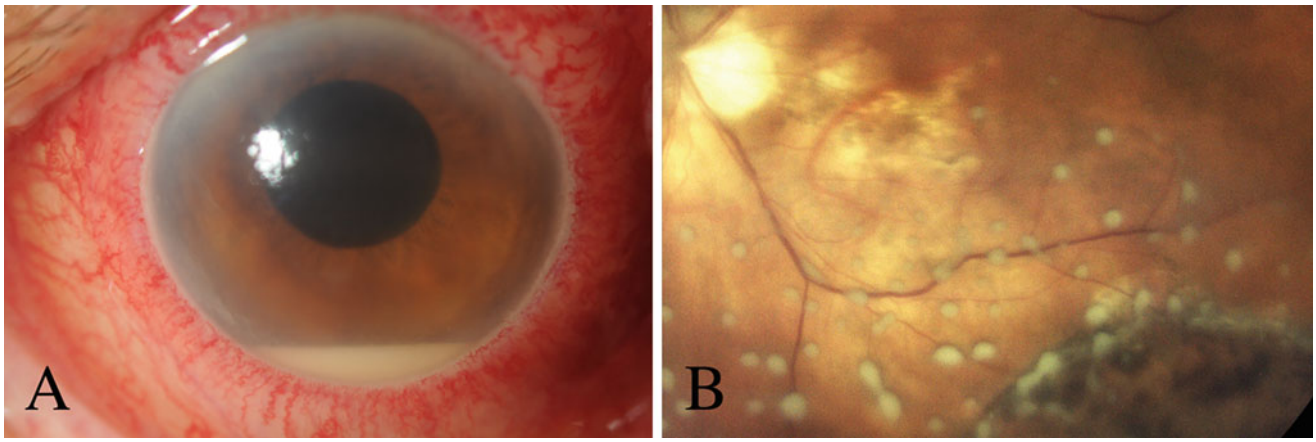

Fig. 8 (**a**) The day after antibiotics therapy onset and steroids discontinuation, the inflammatory reaction worsened and hypopyon was visible at slit-lamp examination. (**b**) Multiple fluffy aggregates were detectable in the vitreous chamber

Suggested Reading

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