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CASE REPORT

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Bilateral endogenous endophthalmitis in a patient after intensive care unit hospitalization for acute respiratory failure due to COVID-19 pneumonia

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ABSTRACT

Purpose: The aim of the study is to present a case of chronic bilateral endophthalmitis in a patient with a history of COVID-19 infection complicated by pneumonia and to discuss new diagnostic options in the field of molecular microbiology.

Summary: A 67-year-old woman reported to the ophthalmology department due to significant deterioration of vision in both eyes in the course of bilateral endogenous endophthalmitis, in order to have a pars plana vitrectomy (PPV) performed. Approximately three months earlier, the patient was hospitalized in the intensive care unit (ICU) for acute respiratory syndrome secondary to pneumonia caused by SARS-CoV-2 infection, confirmed by RT-PCR nasopharyngeal swab. Due to the severe general condition, the breathing was supported by ventilation, central vascular catheterization and a Foley catheter were inserted, and broad-spectrum antibiotics, steroids and antiviral drugs were administered intravenously. In the Ophthalmology Department, posterior vitrectomy was performed in both eyes with collection of vitreous body for microbiological, virological and genetic tests. Using nanopore sequencing, the multifactorial bacterial etiology of right-side endogenous endophthalmitis was established.

Conclusions: A patient with suspected bilateral endogenous endophthalmitis requires urgent ophthalmological consultation, immediate general medical treatment and performance of PPV. Microbiological diagnostics of ophthalmic samples can be extended by whole-genome nanopore sequencing. Unlike traditional cultures, which are often negative, it allows quick identification of microorganisms, even in a small amount of genetic material.

KEY WORDS: endogenous endophthalmitis, COVID infection, nanopore sequencing.

INTRODUCTION

Endophthalmitis can lead to severe deterioration of vision, blindness and even loss of an eyeball within hours of onset of symptoms. There is a predominance (92-98%) of exogenous cases, in which microorganisms enter the eye as a result of insufficiently tight postoperative or traumatic wound, or through an inflamed cornea. Endogenous endophthalmitis accounts for 2 to 8% of all inflammation cases. Endogenous endophthalmitis is a sight-threatening ocular infection presenting as a potential ocular emergency [1-3]. According to the etiology, endogenous endophthalmitis (EE) can be classified as: bacterial (endogenous bacterial endophthalmitis, EBE), fungal (endogenous fungal endophthalmitis, EFE) or mold (endogenous mold endophthalmitis, EME) [4]. It can manifest at any age and is generally due to a hematogenous spread of infection from a remote systemic location, unrelated to prior ophthalmic surgery or trauma (0.04% of patients with bacteremia, 0.5% of patients with fungemia) [5]. A feature of EE is that the infection develops when the patient is immunocompromised. Known risk factors for EE include: recent hospitalization, urinary tract infection, endocarditis, liver abscess, immunodeficient diseases such as diabetes, HIV infection, cancer, neutropenia, renal failure requiring dialysis, intravenous drugs (IVDA), intravascular catheters, long-term antibiotic therapy, steroid therapy and genetic or medical immunosuppression [3, 6-10]. The most common etiology of EBE in Western countries is the gram-positive bacteria streptococci (30-50%, mainly *Streptococcus pneumoniae*, *Streptococcus milleri* and *Streptococcus* A and B) [4], while in the countries of East Asia the condition is most commonly caused by the gram-negative bacterium *Klebsiella pneumoniae* (77%) [10]. The most common cause of EFE in

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Western countries is the yeast-like fungus *Candida albicans* [11-13], which is highly uncommon in East Asian countries. The most common causes of EME are *Aspergillus* and *Fusarium* [4]. Symptoms of EE are usually unilateral [14]. Bilateral cases constitute 14-15% of all EE cases and they are predisposed by presence of bacteria *Meningococcus*, *Escherichia coli* and *Klebsiella pneumoniae* [14]. Symptoms of EE vary in clinical manifestation, ranging from sudden and fulminant in acute cases to mild in chronic cases. These are eye pain, severe visual impairment and eyeball congestion. The diagnosis of endogenous endophthalmitis is based on clinical signs such as: visual deterioration, the presence of anterior and posterior segment inflammation, vitritis, and characteristic posterior segment lesions, vitreous, subretinal exudates. In the history there is a lack of any relationship to surgery or trauma.

Treatment of EE is initially empirical and then modified according to results of culture. It consists in administering general and local antibacterial or antifungal drugs. It has been proven that drugs administered intravenously achieve therapeutic levels in the eye, but the mainstay of treatment is intravitreal drugs [14]. In EBE, the most common intravitreal drugs are vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml), or amikacin (0.4 mg/0.1 ml) [15], while in EFE it is amphotericin B (0.005 mg/0.1 ml). In severe infections, PPV with collection of material for culture, and intravitreal injections are recommended. Review studies suggest that patients who underwent vitrectomy had a 3 times greater chance of preserving vision compared to those who did not [6]. The prognosis for vision improvement in the course of EE is generally poor. It depends on the baseline visual acuity and the causative pathogen. Only 22.2 to 41% of EE cases achieve visual acuity at the finger counting level or better [14, 16]. As much as 55 to 69% of cases terminate with blindness, evisceration or enucleation [6]. EE of fungal etiology is associated with a more favorable prognosis, compared to bacterial EE [17, 18]. It should be emphasized that intensive care unit (ICU) patients constitute a special group with high risk of developing EE due to numerous risk factors. They also include patients with acute respiratory distress syndrome (ARDS) caused by the new virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), requiring intubation. The pandemic of coronavirus disease 2019 (COVID-19) is still affecting a huge population of previously healthy individuals. Some patients develop severe pneumonia with rapid oxygen desaturation requiring urgent hospitalization for respiratory support, intensive care, intravenous drugs, fluids, and steroids, all of which predispose them to secondary infections. (Clinical management of COVID-19. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19). The most common ophthalmic manifestation of COVID-19 is conjunctivitis [19]. Posterior segment pathology including central retinal vein occlusion [20], central retinal artery occlusion [21] and acute macular neuroretinitis [22] have been reported as post-COVID-19 complications. The number of cases of endogenous endophthalmitis have been reported in patients who had recently recovered from severe COVID-19 infection [23]. They had received prolonged steroid therapy in an ICU setting. These patients had initially complained of floaters with blurred vision and had been diagnosed with noninfectious uveitis by their primary ophthalmologists and had received further steroid therapy [23]. One very recent case series from India also described presumed fungal endophthalmitis in four post-COVID-19 cases [24].

A small percentage of critically ill COVID-19 patients develop clinical symptoms of viral sepsis. SARS-CoV-2 viral endophthalmitis has not been described [25].

CASE REPORT

A 67-year-old woman with suspected chronic bilateral endophthalmitis was referred to the ophthalmology department for a consultation, in order to have a PPV performed. Three months earlier, the patient had experienced acute respiratory failure due to pneumonia in the course of SARS-CoV-2 infection and was hospitalized in the ICU. Due to the general condition worsening and the decrease in spO_2 saturation to 50%, she was intubated and ventilated in P-SiMV mode with $FiO_2^{-1} > 0.9$ PEEP + 8 cm H_2O for eleven days, resulting in spO_2 improvement to 95%. A central venous catheter (CVC), peripheral intravenous catheter (PIVC) and a Foley catheter were inserted. The treatment included parenteral nutrition, analgosedation, intravenous hydration, diuretics, catecholamines, steroids, antibiotics (beta-lactam: third-generation cephalosporins, semi-synthetic penicillins, carbapenems, macrolides), monoclonal IgG1 (tocilizumab), anti-viral drugs (remdesivir), anti-thrombotic, sedative and antidepressant drugs. Furthermore, anti-fungal drugs were administered in response to urine culture positive for *Candida albicans* (mixed infection – *Candida albicans* and *Escherichia coli*). Ten days after tracheal extubation the patient was discharged home diagnosed with type 2 diabetes, arterial hypertension, and arrhythmia. Five weeks later, the patient was hospitalized again, in the Department of Internal Medicine, due to pyelonephritis on the left side. She received intravenous antibiotics – fluoroquinolones, aminoglycosides and third-generation cephalosporins. During this hospitalization, the patient reported painless progressive blurring of vision in both eyes for the past several weeks. Ophthalmological examination revealed uveitis in both eyes, not endogenous endophthalmitis. The patient was referred to the ophthalmology department in the place of residence, and then after 3 months from the first symptoms of endophthalmitis to the local ophthalmology department for surgical treatment. On the day of consultation, based on the medical history and clinical image, chronic, bilateral endogenous endophthalmitis with suspected fungal etiology was diagnosed. On the day of admission, baseline BCVA was light perception (LP) without projection in the right eye (RE) and 0.02 in the left eye (LE). On the ocular examination, both eyes were hypotonic (RE 5 mmHg, LE 9 mmHg), painless with mixed irritation, and signs of anterior segment inflammation with keratic precipitates and anterior chamber flare, irregular narrowed

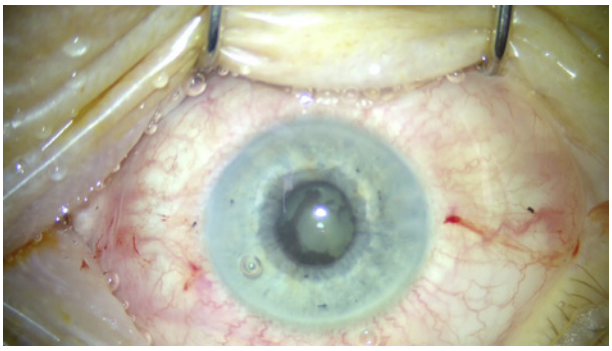

Figure 1. Anterior segment of the LE: Note uveitis, irregular narrowed pupil with posterior synechiae, lens with advanced cortico-nuclear and posterior subcapsular cataract

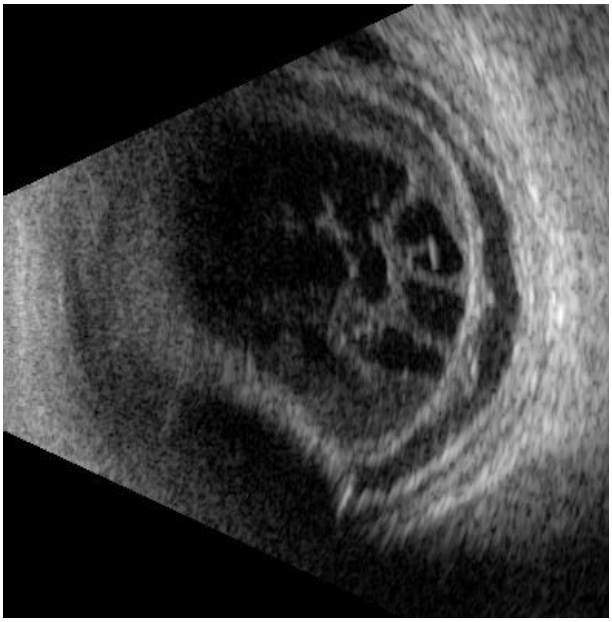

Figure 2. B-scan ultrasound of the RE: Note vitritis, choroidal detachment and old retinal detachment

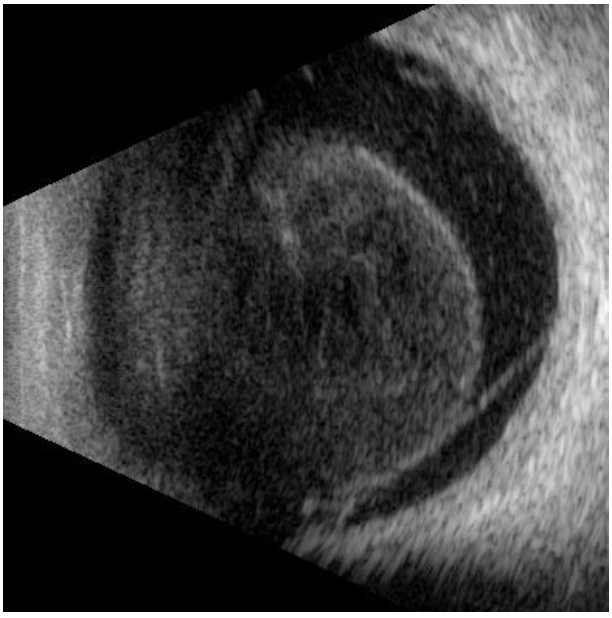

Figure 3. B-scan ultrasound of the LE: Note vitritis and retinal attachment

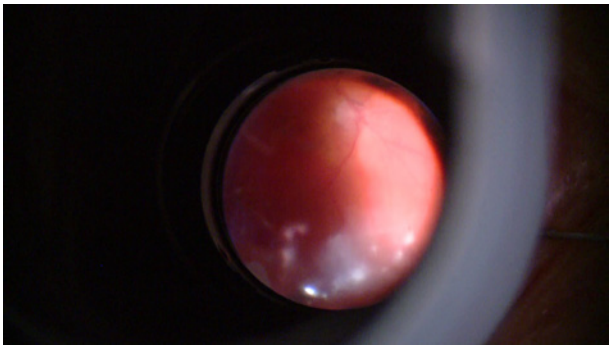

Figure 4. Posterior segment of the LE: Note small numerous spherical, creamy-white balls in the vitreous body and infiltrates in the peripheral part of the retina resembling a fungal infection

pupils with posterior synechiae, lenses with advanced cortico-nuclear and posterior subcapsular cataracts (Figure 1), and hazy vitreous body with densities. The fundus of the RE was invisible, the fundus of the LE was hazily visible: pale optic disc, attached retina, other details were difficult to assess. B-scan ultrasound of the RE revealed vitritis, choroidal and retinal detachment (Figure 2). B-scan ultrasound of the LE showed vitritis and retinal attachment (Figure 3). The patient was referred for pars plana vitrectomy with cataract extraction in both eyes. The LE with better prognosis for vision recovery was operated on first, one day after admission to the hospital. Cataract phacoemulsification with intraocular lens implantation and 23-gauge PPV with 2000 cSt silicone oil tamponade were performed. Intraoperatively, small numerous spherical, creamy-white balls in the vitreous body and infiltrates in the peripheral part of the retina resembling a fungal infection were observed (Figure 4). The whole retina was attached and the macula was normal. Vitreous samples were collected and sent for microbiological (blood agar, Sabouraud agar, chocolate agar, thioglycolate broth), virological (RT-PCR test for SARS-CoV-2 virus) and genetic (nanopore sequencing for the presence of fungi and bacteria) testing. Intravitreal 5% amphotericin B in the infusion fluid (0.1 ml) and intracameral cefuroxime (1 mg/0.1 ml) were administered. Ceftriaxone, fluconazole and dexamethasone phosphate were given intravenously. Ofloxacin, gentamicin, voriconazole, dexamethasone and mydriatic drops were administered locally. After surgery best corrected visual acuity (BCVA) in the LE significantly improved to 0.3. There were no signs of inflammation in the anterior and posterior segment.

The right eye showed no improvement in vision after PPV, was painless and the inflammation lasting over 3 months was stable. Despite this, the decision to operate was taken. Then 2 weeks later cataract phacoemulsification with intraocular lens implantation and 23-gauge PPV in the RE were performed. During cataract removal, posterior synechiae were released, iris retractors and a capsular tension ring were used. The total retinal detachment with the shape of a narrow funnel (PVR grade D-2) with numerous retinal membranes and subretinal abscesses (Figures 5, 6) were visualized after core vitrectomy. The clinical picture of the RE resembled that of a fungal infec-

tion. Vitreous samples were collected and sent for microbiological, virological, and genetic testing. Intravitreal 5% amphotericin B in the infusion fluid (0.1 ml) and intracameral cefuroxime (1 mg/0.1 ml) were administered. The vitrectomy was interrupted and finished because achievement of even temporary attachment of the retina appeared to be impossible. Postoperatively, there was no light perception (NLP) in the RE, and scattered blood in the anterior and the vitreous chamber. Results of the vitreous culture in both eyes for aerobic, anaerobic bacteria and fungi and the RT-PCR test for the presence of SARS CoV-2 virus were negative. Additionally, vitreous samples from both eyes were assessed by means of molecular analysis using whole-genome technology (Oxford Nanopore Technology). The taxonomic identification of bacteria in the right eye was determined. 0.2% of bacteria was obtained in all 254 readings; they were: *Cellulosimicrobium cellulans* (61.42%), *Ralstonia solanacearum* (10.24%), *Escherichia coli* (3.94%), *Staphylococcus aureus* (8.66%). Bacterial genetic material was present in the left eye, but no taxonomic identification was obtained. After 2.5 months, silicone oil was removed from the LE, and simultaneously an intravitreal anti-VEGF drug (aflibercept) was administered due to intraretinal post-inflammatory macular edema (Figure 7). During the 3-month follow-up period, the anterior segment of both eyes was without any signs of inflammation. The LE was painless, with BCVA 0.5, correct intraocular pressure, no macular edema and a fully attached retina. The RE was painless, with NLP, partial blood absorption from the anterior chamber, correct intraocular pressure and no insight into the eye fundus.

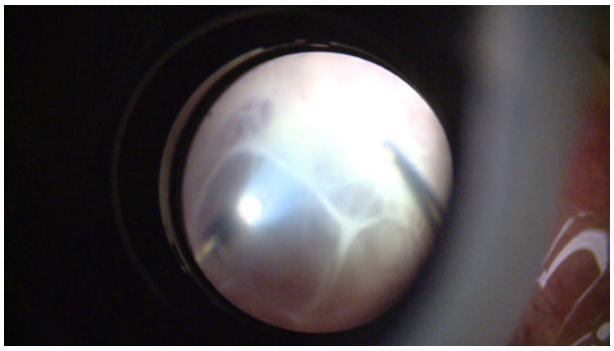

Figure 5. Posterior segment of the RE: Note numerous retinal membranes and detached retina

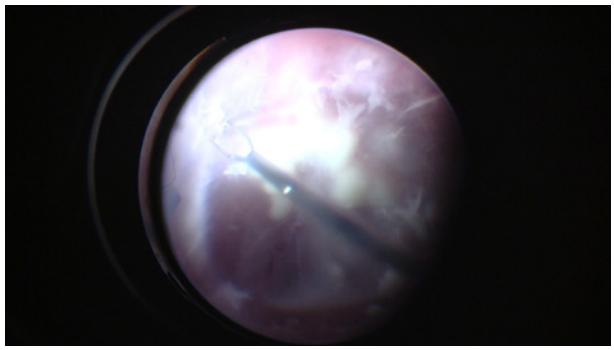

Figure 6. Posterior segment of the RE: Note a few subretinal abscesses and detached retina

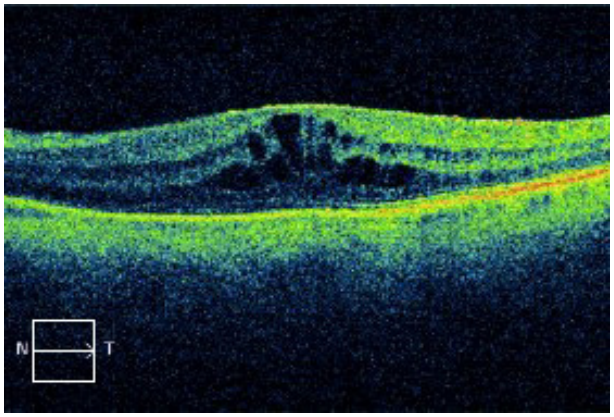

Figure 7. Optical coherence tomography (CARL ZEISS CIRRUS HD-OCT 5000) of the LE: Note the inflammatory cystoid macular edema in the horizontal line of the fundus

DISCUSSION

All physicians of every specialty are currently facing the global health problem of COVID-19, caused by the new SARS-CoV-2 virus spreading by droplets. It should be remembered that the surface of the eye can serve as a gateway for infection and a reservoir for the transconjunctival transmission of viruses [26]. Ophthalmologists are the first to study potentially infectious patients with viral conjunctivitis, which may be the first and only symptom of COVID-19 (0.8% to 31.6%) [27-29], as well as convalescents with ophthalmic complications after ARDS-COVID-19 in the ICU. As a result of metabolic disorders and multi-organ dysfunction, patients have impaired systemic protective mechanisms. The most commonly reported ophthalmic disorders in ICU patients are keratopathy due to incomplete closure of eyelids, conjunctival edema and keratitis; less common are acute primary angle closure (APAC), anterior or posterior ischemic optic neuropathy (AION; PION), central retinal vein occlusion (CRVO) or central retinal artery occlusion (CRAO), as well as mucormycosis (ROCM, rhino-orbital cerebral mucormycosis) [30]. Nearly 60% of critically ill ICU patients suffer from ocular surface disorders, ranging from mild conjunctival irritation to severe keratitis [31]. 77% of sedated and respiratory-assisted patients were colonized with at least one bacterial species other than the normal flora and 40% with multiple ones. The most common isolates were *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Staphylococcus epidermidis* [32]. Acute respiratory distress syndrome (ARDS) is the leading reason for the admission of COVID-19 patients to an ICU. Between 63 and 88% of them require intubation [33-37]. In March 2021, Alper Bilgic and coworkers described three cases of EBE in patients hospitalized due to COVID-19 infection. One of them was found to have SARS-CoV-2 in the vitreous, which is the only published case so far [38]. The patient admitted to our department for posterior vitrec-

tomy developed symptoms of significant visual impairment in both eyes in the previous 3 months, after hospitalization due to COVID-19. We clinically diagnosed bilateral EE, with suspected fungal etiology. The patient had experienced acute respiratory failure due to pneumonia in the course of COVID-19 infection confirmed by RT-PCR test, requiring intubation. She had a general perfect condition before COVID infection, while for the last few months she had been burdened with numerous risk factors for EE, such as several recent hospitalizations, central venous catheter, peripheral venous catheter, tracheal intubation, Foley catheter, urinary tract infection of *Candida albicans* and *Escherichia coli* confirmed by urine culture, parenteral nutrition, immunosuppression associated with severe infection, as well as intravenous drugs from various groups. The first noticeable deterioration in vision in both eyes was reported during the first hospitalization, but ophthalmological examination was not performed at that time. The first ophthalmic consultation took place two months after the onset of symptoms. After 3 months, bilateral endophthalmitis was diagnosed and combined cataract surgery with PPV and intravitreal administration of amphotericin B was performed in both eyes, and silicone oil was given in the LE. Samples of the vitreous body were collected for microbiological (traditional cultures), virological (RT-PCR test for SARS-CoV-2 virus) and genetic (nanopore sequencing) testing. Danielescu, in a metaanalysis (analyzing 31 publications; 2011-2020), noted that PPV in EE was performed in 6.5% to 66% of cases, and second vitrectomy in 3.7 to 37% of cases. Only in 3 publications was this indicator over 70% of cases [39-42]. This may be related to the fact that patients with EE are in a severe general condition and do not receive approval for this procedure. In EE, the fatality rate is high [39]. Considering the fact that the vitreous inoculations in EE are negative in approximately 60% of cases, the decision was made to test vitreous body collected from both eyes using a modern method of next generation sequencing (NGS) in nanopore technology developed by Oxford Nanopore Technologies (ONT). This technology allows analysis of genomes (complete genetic information) of bacteria, fungi, viruses and eukaryotes. In our patient, we used nanopore whole genome sequencing (NWGS) using rapid barcoding technology for the presence of fungi and bacteria, without amplification. Samples of the vitreous body collected from the right eye were subjected to laboratory and bioinformatics analysis, and taxonomic identification was performed. Genetic material of gram-positive bacteria was isolated in 74.02% (*Cellulosimicrobium cellulans* 61.42%, *Staphylococcus aureus* 8.66%) and gram-negative bacteria in 20.08% (*Ralstonia solanacearum* 10.24%, *Escherichia coli* 3.94%); no fungi were found. However, in the left eye it was not possible to determine the pathogen because the amount of DNA obtained after the isolation of genetic material was too small and did not allow for the sequencing stage. Pallen and Didelot report other benefits of WGS. This method increases the range of detected pathogens (viruses, bacteria, fungi, archaea, protozoa), determines taxonomic affiliation and phylogenetic relationships, and assesses potential antibiotic resistance genes and genes related to virulence [43, 44]. Considering the increasing resistance of bacteria to antibiotics, this method should be used more often in the future. In our patient, the vitreous culture for aerobic and anaerobic bacteria and fungi in both eyes was negative, and no SARS-CoV-2 was found in the vitreous. According to published literature, only 14 to 43% of the ophthalmic specimens give positive results of inoculations [6, 45-49].

Cellulosimicrobium cellulans are gram-positive bacteria belonging to the *Promicromonosporaceae* family (*Actinobacteria* type), widely distributed in the mesophilic environment [50, 51]. Two genera of this species, *C. cellulans* and *C. funkei*, are pathogenic for humans. They can cause meningitis, endocarditis, inflammation of soft tissues, joints, endophthalmitis and bacteremia [52]. These infections are rare and occur mostly in immunocompromised people [53, 54]. In 2019 Maria Rivero published data from a literature review on infections caused by *Cellulosimicrobium*. The most common source of infection was bacteremia associated with central venous catheterization [55].

Ralstonia solanacearum (synonym *Pseudomonas solanacearum*, *Burkholderia solanacearum*) is a gram-negative bacterium present in soil and in the aquatic environment. It belongs to the category of human opportunistic pathogenic bacteria of low pathogenicity. It can appear in hospitalized, immunocompromised and critically ill people. It may cause bacteremia associated with CVC, pneumonia, meningitis, and bone marrow inflammation [56]. Several cases of infections of that etiology [57] and a single paper on nosocomial infection in 34 patients whose infection and bacteremia was caused by intravenous administration of infected normal saline have been published so far. *Ralstonia solanacearum* is susceptible to quinolones, penicillins, third-generation cephalosporins, carbapenems and trimethoprim-sulfamethoxazole, and it is resistant to aminoglycosides [58]. It is a pathogen little known to clinicians and impossible to detect in traditional cultures; it can be detected only by means of PCR, with specificity for several *Ralstonia* species of 99-100% and, as in our clinical case, by nanopore sequencing. During hospitalization, the described patient received prophylactic intravenous third-generation cephalosporin with a broad antibacterial spectrum. It is active against aerobic gram-positive bacteria (*Staphylococcus aureus* MSSA, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*) and against aerobic gram-negative bacteria (*Borrelia burgdorferi*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Moraxella ganisidisorrhoea*). Due to the improvement of the local condition, the treatment was not modified after obtaining a positive sequencing result. Poor final visual acuity in the RE and good final visual acuity in the LE was obtained. According to the publication, in EBE the prognosis is worse for gram-negative bacteria than for gram-positive ones [47]. Of gram-positive bacteria, the worst prognosis is associated with group B *Streptococcus* [59]. Danielescu and colleagues determined a better prognosis of EE for baseline visual acuity allowing at

least counting fingers, pars plana vitrectomy (ppVE), intravitreal administration within 24 hours of clinical diagnosis, and the presence of a focal nature of EE [39]. In spite of a two-month delay in diagnosis and surgical treatment due to EE the patient reached good BCVA in the LE (0.5).

CONCLUSIONS

In an ICU patient with ARDS caused by a systemic infection, reporting visual disturbances, the risk of endogenous endophthalmitis should be taken into account. Therefore, these patients require urgent ophthalmic consultation. If endophthalmitis is suspected, the patient must undergo general and surgical treatment as soon as possible. Performing posterior vitrectomy even at a time delayed from first symptoms' onset gives a chance to obtain functional visual acuity and preserve the eyeball. In the search for pathogens causing endogenous endophthalmitis, diagnostics using traditional methods of detecting microorganisms are often ineffective. A more complete diagnostics may be obtained thanks to the use of new methods in the field of molecular microbiology. Whole genome nanopore sequencing allows one to identify the pathogen even with a small amount of genetic material, and to detect rare microorganisms.

DISCLOSURE

The authors declare no conflict of interest.

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