

The Importance of Fluconazole in Treatment of Endogenous Endophthalmitis in Patients Prior Treated Using Negative Pressure Therapy for Wound Closure Contaminated with Methicillin-resistant *Staphylococcus aureus*

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Severe infections with C. albicans should be treated promptly with antifungal agents, any delay in treatment increases the risk of endophthalmitis. The systemic Amphotericin B therapy is the gold standard in the treatment of endophthalmitis, but in the case of fungal infections it has not yet been determined. Numerous studies have shown that the use of Fluconazole is effective in the treatment of fungal endophthalmitis. In this paper, we report two cases (3 eyes) that have been presented for the same accusations of significant decrease of AV (visual acuity), ocular pain and blepharospasm suddenly installed, both of which required urgent antibiotic and intravenous antifungal treatment. Both are diagnosed with endogenous endophthalmitis and vitreous biopsy + VPP (pars plana vitrectomy) are performed, with a negative result of the vitreous culture. In both situations the treatment was with antibiotic and systemic antifungals. Postoperatively, evolution was favorable in the first case and less favorable in the second one. The prognosis depends on the virulence of the microorganisms and the time elapsed until initiation of the treatment. Also, the presence of risk factors such as diabetes, sepsis, recent abdominal surgery (C. Albicans is part of the comensal flora of the digestive tract) have influenced the prognosis decisively. Severe infections with C. albicans should be promptly treated with antifungal agents, any delay in treatment increases the risk of endophthalmitis. Even when prolonged treatment of candidemia is instituted, 3% of patients can develop endogenous endophthalmitis, so ocular evaluation is particularly important for patients immobilized in anesthesia and intensive care units.

Keywords: fluconazole, endogenous endophthalmitis, candida albicans, negative pressure therapy

Endophthalmitis is an inflammation involving intraocular tissues (vitreous and anterior chamber) in response to endogenous, exogenous infections, trauma, tumors, immune and vasculitis reactions. Patient hygiene and surgical sterility are the most important measures of endophthalmitis prophylaxis [1].

The endogenous form of endophthalmitis is determined by the hematogenous dissemination of microorganisms, representing 2-8% of the total endophthalmitis. In patients with a compromised immune system and the presence of risk factors such as diabetes, systemic lupus erythematosus, HIV infection manifestation of endophthalmitis is favored. Gastrointestinal surgery, endoscopy and dental procedures can also increase the risk [1, 2]. Fungal endophthalmitis develops slowly with focal or multifocal areas of corioretinitis. The most common etiology is that of candidiasis, 37% of patients with candidemia have been reported with endophthalmitis [3].

The diseases associated with candidiasis and the development of intraocular infection include hospitalization with a history of recent major gastrointestinal surgery, bacterial sepsis, systemic use of antibiotics, use of localized catheters, hyperalimentation, debilitating diseases (diabetes mellitus), immunomodulatory therapy, prolonged neutropenia, organ transplantation, or a combination of these [1,3].

Experimental part

Case 1. We present the case of a 61-year-old female patient in the urban environment who was admitted in the I Ophthalmology clinic accusing the decrease in visual acuity at both eyes (AO), ocular pain, congestion, blepharospasm and hyperlacrimation, suddenly installed. From the personal pathological history we remember: admission to the general surgery clinic when practicing for gastric adenocarcinoma - total gastrectomy two months ago. The postoperative progression was favorable, being discharged. When the patient came at control as it was scheduled the clinical exam revealed a collection of 4/3/3cm on the incision line which was drained. The patient also showed right pluris and anemic syndrome (haemoglobin=9g/dL). The antibiotic sample identifies Methicillin-resistant *S. aureus* (MRSA) and wide-spectrum antibiotics were initiated until the result is obtained. It is chosen to close the wound using negative pressure therapy and gentamicin instillation (sensitized). Negative antibiogram was obtained 8 days after the initiation of therapy, and the negative pressure therapy kits were changed to a 48-h interval. The wound has considerably reduced its size by imposing its suture with only two separate suture threads. The patient is subsequently admitted to the pneumology service for further treatment,

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totaling 20 days of hospitalization. The specialty examination finds the following: visual acuity VAOD= 1/50fcnc si VAOS=nd/30cm. Anterior pole highlights at both eyes (AO): Conjunctival hyperaemia, Tyndall2 + OD, hypopion OS, AO irias synechiae, at lens level the pigment is present on the anterior capsule, disorders of lens transparency [figura 1]. The AO eye exam reveals: numerous whitish conglomerates in vitreous predominantly at the posterior hyaloid, whitish retinal lesions, round disposed across the posterior pole and the mean periphery (fig. 2)

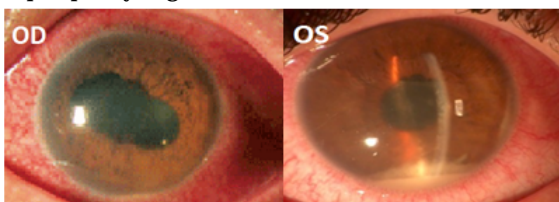


Fig. 1. Case 1. Biomicroscopic appearance of the previous pole

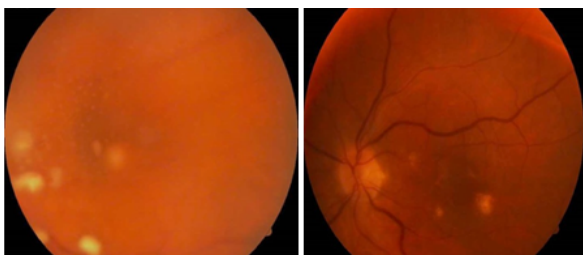


Fig. 2. Case 1. Appearance of the bottom of the eye at admission

Mode B ultrasound revealed multiple mobile whitewashed membranes that occupy the entire vitreous cavity, specific to endophthalmitis (Figure 3). Endogenous endophthalmitis is diagnosed and Vitrectomy by pars plana (VPP) biopsy at right eye is performed associated with 360 degree endolaser and at 2 weeks the same procedure was done at left eye. Postoperatively visual acuity increased to 0.8 cc ++ 1sf at right eye and left eye at 0.6cc + 1.5.

Case 2. It is a 62-year-old patient who was admitted for the same symptoms, suddenly installed in the OS. From the personal pathological history we note: grade IV obesity, type II diabetes mellitus, hypertension, urinary infection (with Candida albicans). The patient is admitted to the 2nd Surgery Clinic, Sf.Spiridon lasi in November 2014, when gastric banding for obesity was practiced. The postoperative progression was favorable. Due to non-

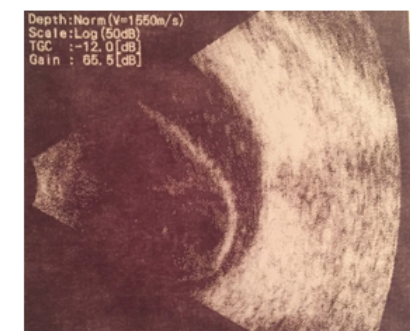


Fig. 3. Case 1. Ultrasound appearance in B mode

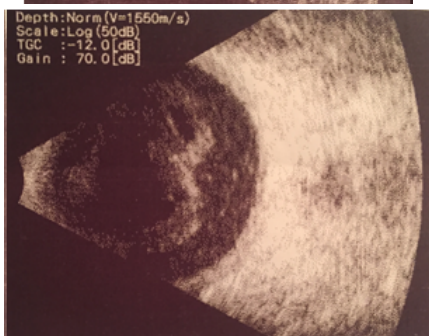


Fig. 4a. Appearance after first vacuum exchange kit



Fig.4b. Bridge technic

compliance with anticoagulation therapy at approximately 3 weeks the patient is in emergency with masive bilateral pulmonary thromboembolism, being admitted to the Cardiology clinic where, under conservative treatment, evolution is favorable. In October 2015, the patient returns to emergency, presenting upper digestive haemorrhage, haemorrhagic shock, for which after paraclinical investigations she undergoes a surgical intervention: exploratory laparotomy, exploratory gastroduodenotomy, gastric banding suppression, drainage. The antibiogram taken from the gastrocamera revealed the presence of MRSA for which negative pressure therapy with gentamicin instillation was opted for. The Bridge technique (aspiration drainage of multiple cavities) was used to close both parietal defects (Xifoombilical incision fig. 4a and gastrocamera site fig.4b). The postoperative progression was favorable with the closure of parietal defects at 12 days of use of negative pressure therapy. Antibiotic negative reading was obtained after 9 days of negative pressure therapy.

The ocular examination finds the following: visual acuity (AVOD = 1fcnc, AVOS = nd / 30mm), intraocula pressure (PIOAO = 11mmHg). Anterior biomicroscopy: OS diffuse conjunctival congestion, diffuse epithelial edema, Tyndall 2+, posterior iritis (SIP), pigment on anterior capsule, lens opacity disturbance (fig. 5).

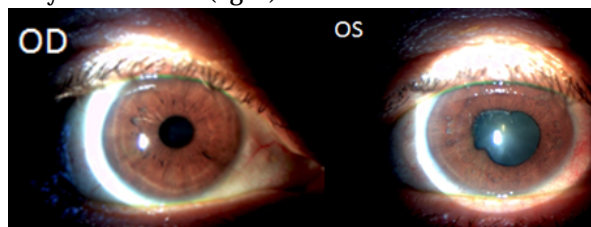


Fig. 5. Case 2. Biomicroscopic appearance of the previous pole

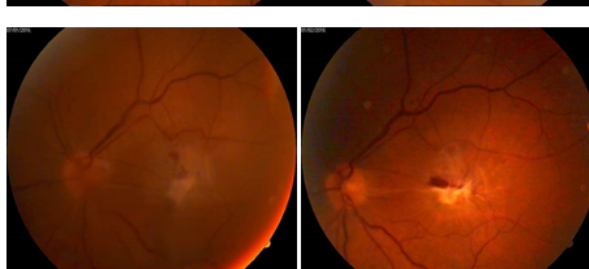


Fig. 6. Case 2. Appearance of the bottom of the eye at admission (first two pictures) and 2 months after surgery (last two pictures)

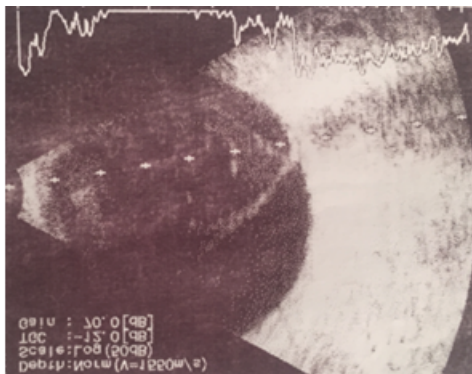


Fig. 7. Case 2. The echographic appearance of A + B mode on the left eye

Fundus Eye exam at :OD normal appearance, OS: fibrosis in the macular area that makes the joint with the retina, punctual bleeding adjacent to the fibrosis area, vitreoretinal membranes that tract the macular area; inflammatory reaction of the predominantly inferior glass-like vitreous with snowball appearance (fig. 6). These clinical elements have also been confirmed by OCT (ocular computer tomography). Two months after treatment, an area of subretinal fibrosis in the macula with adjacent haemorrhages, macular traction and peripapillary splitting bleeding is highlighted in OS (fig. 6, the last two photographs). Mode B ultrasound highlighted multiple blunt membranes that occupy the entire vitreous cavity, specific to endophthalmitis (fig. 7). Endogenous endophthalmitis is diagnosed and VPP biopsy at OD is performed associated with 360 degree endolaser associated with membrane peeling. Postoperatively visual acuity increases to 4/50 fncn, with slow favorable evolution.

In both cases hemoculture and vitreous biopsy were negative. It is established a systemic treatment regimen with Fluconazole 200mg/day, Vancomycin 1g/12h interval, topical Netildex, Tropicamid 1picx4 / day, with slow favorable evolution (fig. 8). Fluconazole therapy was initiated for a minimum of 2 months, maintaining the same therapeutic dose, with favorable functional outcomes. The prognosis of the two diseases depends on the virulence of the micro-organism, the degree of ocular damage and the time elapsed until treatment initiation. The presence of risk factors such as diabetes mellitus, sepsis, neoplasia, recent abdominal surgery (*C. albicans* is part of the comensary flora of the digestive tract), systemic antibiotic therapy has decisively influenced prognosis.

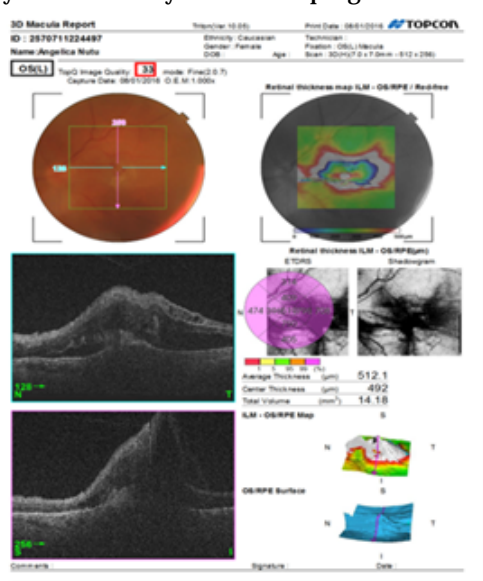


Fig. 8. Case 2. The OCT aspect that highlights the presence of important macular edema

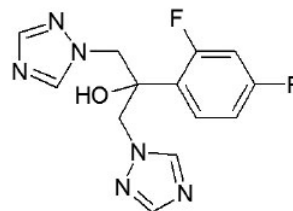


Fig. 9. Structure of fluconazole [4]

Results and discussions

Endogenous endophthalmitis is a rare entity that affects individuals regardless of age. The endogenous form of endophthalmitis is determined by the hematogenous dissemination of microorganisms. In patients with a compromised immune system and the presence of risk factors such as diabetes, systemic lupus erythematosus, HIV infection is favored endophthalmitis.

Hyperglycaemia is an initiating event leading to a series of metabolic changes that may originate from increased oxidative stress [5]. The hyperglycemia induced by increased oxidative stress and receptor for advanced glycation end products (RAGE) activation increases the activation of transcription factor- jB (NF- jB) in endothelial and vascular smooth muscle cells. This transcription factor regulates the expression of the genes encoding a number of mediators of atherogenesis such as leukocyte-cell adhesion molecules and chemoattractant proteins that recruit lymphocytes and monocytes into the vascular wall.

Activation of the NF jB pathway may also cause a switch of the endothelial functions toward a prothrombotic condition that, together with an altered platelet metabolism and intraplatelet signaling pathways and with the inflammatory syndrome, contributes to the pathogenesis of atherothrombotic complications in diabetes mellitus [6]. Also, oxygen free radicals (superoxide anion, hydroxyl radical etc) produced in excess stimulate lipid peroxidation of the polyunsaturated fatty acids forming, thus, in excess, lipid-peroxil radicals [7]. The presence of inadequate glycemic control may be involved in the probable mechanism of endogenous endophthalmitis. Anemia is a common complication of malignancy occurs in almost 50% of patients with solid tumors and more frequently in those with blood diseases - cancer: myeloma, leukemia and lymphoma [8].

The disorders associated with fungal endophthalmitis include hospitalization with a history of recent major gastrointestinal surgery, bacterial sepsis, systemic use of antibiotics, and the use of localized catheters [3,9]. Both presented cases were admitted to the Surgery Clinic with a large number of days of hospitalization during which surgery was performed that targeted the digestive tract. Some studies confirm the appearance of endogenous fungal endophthalmitis after recent surgery. Paulus et al., in a prospective study involving 124 patients with fungi, identified a 1.6% endogenous endophthalmitis rate, a identified risk factor being prolonged hospitalization and parenteral therapy, but statistically insignificant [3].

Fungal endophthalmitis is an ocular infection that threatens the vision and appears most frequently as a result of infection. The correct diagnosis of endophthalmitis etiology and appropriate treatment can influence vital and functional prognosis.

It is known that antifungal therapy is the gold standard of endophthalmitis, but there is no consensus about the specific treatment of ocular candidiasis. Studies have shown that patients respond well to Fluconazole therapy systemically. Michelle E. Akler and colab. initiated fluconazole therapy at 200 mg / day p.o in 14 patients (16 eyes) with candida endophthalmitis for 2 months, obtaining healing at 94% (15 out of 16 eyes).

In addition, fluconazole was used in combination with pars plana vitrectomy for the successful treatment of four cases of candidal endophthalmitis that were complicated by moderate to severe glaucoma [10,11]. Similar to this study and our patients, Fluconazole therapy, given at 200 mg / day, associated with vitrectomy by pars plana has been successful in both the first and second cases. In line with literature studies, Fluconazole therapy appears to be safe and effective as an alternative or addition to the treatment of endophthalmitis with candida [10,11] A number of studies have demonstrated the benefits of negative pressure therapy in the treatment of infected wounds, showing superior efficacy compared to conventional dressings [12].

Microbiological surveillance of the wound after initiation of negative pressure therapy was shown to significantly improve the evolution, with an important reduction in the contamination of the wound. From a clinical point of view, necrosis was produced in a limited number of cases, obvious remission of SIRS and hiperatabolic syndrome was observed [13]. Successful healing of wounds, spontaneous or after surgery, is correlated with the bacterial load of the affected tissue which must be less than 10⁶ bacteria per gram of tissue. Bacterial accumulations greater than 10⁶ interfere with wound healing.

Studies have certified decreased bacterial load of the wound for about 20% of patients in the four days of the establishment of negative pressure therapy and 60% of patients in 8 days after start of treatment. Studies of Morykwas and Argenta, Banwell et al. and Morykwas et al. have reported increased clearance of bacteria from the infected wound by using negative pressure therapy.

Conclusions

Severe infections with *C. albicans* should be treated promptly with antifungal agents, any delay in treatment increases the risk of endophthalmitis. Even when prolonged treatment of candidemia is instituted, 3% of patients can develop endogenous endophthalmitis, so ocular evaluation is particularly important for patients immobilized in anesthesia and intensive care units. Fluconazole therapy appears to be safe and effective as an alternative or addition to the treatment of endophthalmitis with candida

The role of wound micromediation in response to mechanical influence has gained the attention of both clinicians and researchers interested in the wound healing process. Mechanical forces have been used for centuries to create tissue, but it must be borne in mind that the application of excessive mechanical forces leads to their destruction. Optimizing wound healing involves many variables among which the first and most important is the visualization and identification of agents that compromise the host in the healing process.

Factors such as edema / exudate, bacterial burden, unviable tissue, glycemic control, and nutritional support should be specifically addressed to each patient and

wounds in part before using various dressings and topical agents.

In the future, we hope we will have data to help select optimal parameters for specific injuries, including the optimal user interface material according to the needs of each wound.

The abusive use of antibiotics negatively impacts both patients and the health care system, and is detrimental to the cost benefit balance on the long term.

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