FOLLOW-UP ABOUT TWO CASE REPORTS AFTER POSACONAZOLE THERAPY

Authors:

Luigi Tarani[1]
E-mail: *luigi.tarani@uniroma1.it*

Francesca Silvestri[1]
E-mail: *francesca.silvestri89@gmail.com*

Gioella Iaci[1]
E-mail: *gioella.iaci@gmail.com*

Francesca Patriarchi[1]
E-mail: *francescapatriarchi@libero.it*

Debora Rasio[2]
E-mail: *debora.rasio@gmail.com*

Annalisa di Coste[1]
E-mail: *dicoste.annalisa@gmail.com*

Marzia Duse[1]
E-mail: *marzia.duse@uniroma1.it*

Costantino F.[1]
E-mail: *costantinofc@libero.it*

[1)] Dipartimento di Pediatria e Neuropsichiatria Infantile, Sapienza Università di Roma

[2)] Dipartimento di Medicina Clinica e Molecolare, Sapienza Università di Roma

ABSTRACT

Zygomycosis is a rare opportunistic fungal infection that often complicates patients with uncontrolled Diabetes Mellitus, primary and acquired immunodeficiencies as defects of the cell-mediated immunity, myelodysplastic syndrome, hematological malignancies undergoing chemotherapy, HIV and long term therapy with steroid [1]. Mortality rate of these patients is very high, up to 85% [2].

The causative organism is an aerobic saprophytic fungus, releasing spores, belonging to the order of Mucorales of the class Zygomycetes [3]. Inhalation and direct contamination of skin lesions are the major causes of infection, so the sporangiospores can migrate up to the lungs, nasal cavity and paranasal sinuses, gut and cutaneous tissues causing primary infection, hyphae invade vessels producing thrombi. Rhinocerebral Zygomycosis occurs with cranial nerve palsies, eye proptosis, pain and often blindness. Zygomycetes can invade central nervous system (CNS) from paranasal sinuses or remote site of infection [1].

This life-threatening infection could be defeated through early detection, surgical excision and appropriate debridement, aggressive antifungal therapy, and control of risk factors, like diabetes mellitus in our cases.

We reported the follow-up after long term therapy with Posaconazole in two Italian girls with Diabetes Mellitus Type 1 previously published [1,4].

KEYWORDS: Rhino cerebral Mucormycosis; Posaconazole therapy; Pediatric.

1. CASE REPORT NR. 1 AND FOLLOW-UP.

Rhinocerebral zygomycosis in a 14-year-old girl with uncontrolled type 1 diabetes mellitus occurred with dental pain, facial swelling and ecchymosis of left periorbital region with decreased visual acuity and colour vision, unresponsiveness to antibiotic therapy with amoxicillin. Physical examination and electromyography showed a severe VII nerve damage.

Radiographic examination showed haziness of the left maxillary sinus with erosion of the lateral sinus wall. MRI of the patient's head revealed a marked mucosal thickening of the left maxillary sinus extended to the sphenoid, ethmoid and frontal sinus with moderate inflammatory effusion (Figure 1). After surgery debridement of the inflammatory tissue, the tissue biopsy showed aspecific inflammatory infiltrate by fungal species belonging to the Zygomycetes. The patient was treated for 20 days with imipenem, teicoplanin, metronidazole and acyclovir, and then she was treated with intravenous liposomial amphotericin B (L-AMB) for 10 days to which posaconazole (POS) 800 mg/day in association with its caspofungin: echinocandins, was immediately replaced, due to the onset of side effects such as hypotension, hypokalemia and profuse sweating. This important infection led to optic nerve atrophy and palsies of the 7th cranial nerve, hesitation in the left eye, blindness and ipsilateral facial paralysis.

After 4 months, during a new admittance to our pediatric department for fever (T 39 °C), blood examination showed an increase of inflammatory markers and elevated aminotransferase which lead us to test serology and DNA for EBV and CMV in plasma and urine. DNA- PCR for CMV detected decreased 170.056 viral copies/ml during the follow-up without treatment. The follow-up MRI showed progression of the infection with significant intracranial extension, involvement of the neurovascular retromandibular axis and left cavernous sinus with occlusion of ipsilateral cavernous carotid and increased signal of the walls of the left middle cerebral artery caused by arteritis [1]. L-AMB was reintroduced (3 mg/kg iv) for 3 days a week, in association with Posaconazole 800 mg/day per os in four doses. To improve her glycemic control it was necessary to replace multi injecting

insulin treatment with insulin pump treatment associated with continuous glucose monitoring. The girl was under close clinical monitoring as the renal function was detected to be at high levels: Creatinine 2,3 mmol/L (n.v. 0,5-0,9 mmol/L), Urea 76,1 mmol/L (n.v. 1,8 -6,4 mmol/L) so she started therapy with enalapril 5mg/day.

After the article published by di Coste et al. in 2013 [1], during follow-up, the brushing of the left maxillary and sphenoid sinus to culture for mycetes was negative.

So, after one year of treatment with L-AMB, considering the deterioration of the renal function, and the collateral effect on our patient, it was reduced up to 3 mg/kg ev for three times a week up to the end of the treatment, continuing POS. After 6 months of POS therapy, the follow-up MRI detected a reduction of inflammatory tissue, and no progression or reactivation of the fungal infection and Posaconazole was suspended. At 12 months of follow-up she was tested with a nasal swab that detected the presence of a fungal infection by Aspergillus Niger. The endoscopy of the upper airways showed "diffuse edema of nasal mucosa, mucus secretions in the anterior ethmoid region and edema in the left ethmoid region". So, she started an antifungal therapy per os with Voriconazole initially from 200 mg 3 times a day, then twice a day until once a day, within three months. The last HbA1c was 6,7 % mg/dl (50 mmol/mol). The last MRI to date detected "minimal residual tissue thickening, minimal inflammatory thickening of left maxillary sinus. Unchanged angiographic framework showing lack of representation in the left internal carotid artery flow".

1.1 CASE REPORT NR. 2 AND FOLLOW-UP.

A 12-years old girl with beginning diabetic ketoacidosis (DKA), on the third day of recovery, developed fever, nasal dense secretion, and a swelling of the left orbita, with proptosis, ophthalmoplegia, and unilateral blindness. After empirical antibiotic therapy, a genus of fungi – Rhizopus spp. belonging to the class of Zygomycetes, was detected, and the patient started a therapy with Amphotericin B. Doses were increased in steps, up to 10 mg/kg/day. Also, hyperbaric oxygen therapy was performed every 2 days to oxygenate perinecrotic tissues. Because of the progression of the

fungal disease with loss of sight of her left eye and no observed improvement, on the 12th day a nasal and left maxillary sinus surgical debridement was performed and amphotericin B therapy was replaced with new triazole POS. The initial daily dose was 5 mg/kg t.i.d with fatty food for 3 weeks, followed by a daily dose of 10 mg/kg in four doses for 2 months, and then 20 mg/kg/day in four doses for 16 months, and in two doses for further 5 months.

The therapeutic regime was progressively modified to obtain the best equilibrium among tolerability, efficacy, and compliance [4].

The patient rapidly benefited within 10 day, with reduced swelling and pain and good control of her glycaemia. An MRI scan performed three months later was negative. Except for the sight loss of the left eye (Fig. 2), 15 months after POS start, the ethmoidal sinuses were still affected. Therefore, due to side effects related to POS like elevated liver enzymes, prolonged QT intervals, nausea, and headache, which were checked up every 3 months, but were not recorded, the therapy was considered almost completely effective with only the ethmoiditis remaining for treatment and it was prolonged with a total of 2 years of treatment. 6 months after ending therapy, the the girl is in good health conditions and her monthly nasal cultures, performed in a different laboratory, have been negative for Zygomycetes [4].

After the article published by Tarani et al. in 2008 [4], to date, our patient is in good health and carries out regular medical checks. The patient needs periodic endoscopic cleaning of the nasal cavity and paranasal sinuses to remove crusts because of the previous surgical debridement to eradicate the infection that altered the correct mechanical ventilation with nasal crusting and lack of air humidification and absence of air vortex formation. Nasal swabs were always negative. Fundus examination shows no signs of diabetic retinopathy. The patient performs multi injection insulin therapy with Degludec and Lispro with good glycemic control, last HbA1c was 6,7% (50 mmol/mol). The last tests showed microalbuminuria 50 mg/l (n.v. 20 mg/l, creatinin clearance 71 ml/min (n.v. 95-160 ml/min), azotemia 37 mg/dl (n.v. 15-50 mg/dl), creatinine 0,7 mg/dl (n.v. 0,6-1,1 mg/dl). The patient doesn’t undergo any MRI scans anymore because she is in

good health without signs or symptoms of fungal reinfection.

2. DISCUSSION

This aggressive fungal infection mainly affects patients with uncontrolled diabetes because of the high availability of glucose and the pathogen's ability to assimilate carbohydrates, to grow at temperatures greater than 37°C, the lower response of T-cells, the reduced serum inhibitory activity against the Rhizopus in lower pH and the increased expression of some host receptors that mediate the invasion of human epithelial cells by microorganisms.

Rhinocerebral zygomycosis has characteristic signs of onset: cranial nerve palsies (66.7% of cases), facial/eye swelling or blindness (40%), eye proptosis (33.3%), periorbital cellulitis or pain (20%), epistaxis, headaches, nasal discharge, decreasing consciousness, dysarthria and otalgia (6.7%) [1].

Posaconazole (POS) is a second generation triazole antifungal agent; it is a lipophilic molecule, structurally related to itraconazole and exerts the azole's mechanism of action, i.e., it inhibits the ergosterol production by binding and inhibiting the lanosterol-14-a-demethylase that is present in almost all fungi but not in Pneumocystis. [5,6,7].

The drug has broad spectrum activity against Candida species, Aspergillus species, Cryptococcus Neoformans, the Zygomycetes, also those resistant to other azoles and other filamentous fungi [6]. POS is actually the most potent azole in refractory invasive fungal central nervous system (CNS) disease, Zygomycetes included [8]. The dose of POS for adults and for children above 13 years is 200 mg orally t.i.d. for the prevention of invasive fungal infections and q.i.d. for the treatment. The pediatric dose below 13 years in reported cases, was given at a mean daily dose of 10 mg/kg (maximum 40 mg/kg/d) in four divided administrations [4,9].

We used L-AMB because the conventional AMB is more toxic and several studies suggest that L-AMB could be a first line or salvage therapy. Association between L-AMB and Posaconazole is more effective against the rhinocerebral zygomycosis, improving the survival rate of patients. Perhaps the only therapy with L-AMB could be failed, so the new azole therapy is most aggressive

and specific without several collateral effects.

Voriconazole, used in the first patient, is the most effective azole therapy against Aspergillus infection without activity against Zygomycetes. [8].

Definitive diagnosis should be made by clinical manifestation of the disease, histopathological examination of infected tissues, culture (culture studies are usually unsuccessful), and radiographic features. Mortality rate from mucormycosis is high in spite of the antifungal therapy.

3. CONCLUSION

In the literature there is no standard and specific consent on how long the therapy with LAmB in association with POS should last but you must "sail in sight" through performing MRI and fungal cultures during the follow-up. In fact, the first patient's treatment lasted one year, while the treatment of the second patient lasted two years.

Studies show an average duration of therapy in adult patients with POS of about 12 months at a dose of 800 mg/day. Patients who received therapy with POS for more than a year had an increased value of creatinine, while L-AmB is more toxic than POS [10]. In fact POS is a salvage therapy in patients who have had adverse reactions to the L-AmB [11]. Cornely OA et al. [12] points out that the choices for first line treatment in neonates, children and adolescent include L-AmB, which for pharmacokinetic and pharmaco-dynamic reasons is the preferred drug for infections involving the CNS. POS and the combination of L-AmB plus caspofungin are only recommended with marginal strength for first-line therapy of pediatric patients. In our cases the therapy with L-AmB associated with POS was effective and the duration of therapy was chosen in relation to the clinical health and their follow-up, even if we have adopted the same strategy of therapeutic regimen of adult patients because of the absence of safe data in pediatrics population. Our second patient underwent two years of POS therapy which is one of the longest therapies reported in the literature without complications.

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