Management of obstructive renal failure caused by bilateral renal aspergilloma in an immunocompetent newborn

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Fungal infection of the kidneys is a rare condition that has been reported in premature babies and in diabetic or immunocompromised adult patients. Candida spp. is the most frequent microorganism involved. This paper reports a case of an immunocompetent newborn with a bladder exstrophy who suffered from an acute renal failure caused by bilateral renal aspergilloma (Aspergillus flavus). The newborn was treated with amphotericin B urinary tract irrigation through bilateral nephrostomy catheters, combined with liposomal amphotericin B and voriconazole therapy, which improved his renal function. However, due to persistent fungal colonization, a long antifungal treatment and permanent ureterostomies were necessary to deal with new episodes of ureterorenal obstruction. As of November 2009, despite the renal injuries, renal function had been conserved. The management of the mechanical obstruction and the choice of antifungal drugs are discussed in this unusual case.

Introduction

The incidence of invasive aspergillosis has increased due to the rising number of immunocompromised patients in recent years. Invasive aspergillosis in children younger than 3 months has been related to prematurity, skin trauma, corticoid exposure and chronic granulomatous disease (Groll et al., 1998). According to the literature, the lung is the organ mostly involved (Burgos et al., 2008). Concerning the kidneys, the most common involvement is metastatic lesions as sequelae of Candida fungaemia, which is especially frequent in diabetic or immunocompromised patients. This characteristic has also been found in newborns, above all in those with risk factors such as prematurity, where broad-spectrum antibiotics and intravenous catheters are used (Vazquez-Tsuji et al., 2005; Bell et al., 1993; Hari et al., 1997). Only few cases of renal aspergillosis have been described, all in diabetic adults, intravenous drug users and immunocompromised patients. In children, this has hardly ever been reported (Perez-Arellano et al., 2001; Smaldone et al., 2006; Kueter et al., 2002).

Aspergillus flavus is a filamentous fungus that has spread worldwide. It grows as a saprophyte in soil forming part of the air. It is known for its pathogenicity in immunocompromised patients, leading to different forms of invasive aspergillosis (Hedayati et al., 2007). We present a case of an immunocompetent newborn suffering from a bladder exstrophy, who developed an obstructive acute renal failure caused by A. flavus bilateral renal aspergilloma.

Case report

A male newborn was admitted to the Neonatal Intensive Care Unit of Carlos Haya University Hospital, Malaga, with a diagnosis of postnatal exstrophy bladder, epispadias and anal–rectal anomaly. Surgical intervention was performed on the first day, where guide catheters were placed in both ureters and the bladder. Two days after surgery, various empiric antibiotic regimens were gradually implemented due to a suspicion of sepsis. Also, a 2 day treatment with methylprednisolone (1 mg kg\(^{-1}\) per day) was added to the regime. As the newborn’s progress was favourable, he was referred to the ward with only the urethral catheter remaining.

Twenty-one days after surgery, anuria was detected after an accidental displacement of the urethral catheter. An
attempt to replace the device induced a cardio-pulmonary arrest whilst the child was in the operating theatre, followed by an acute anuric renal failure. Mechanical ventilation and peritoneal dialysis were performed in the Pediatric Intensive Care Unit. At that moment no urine sample could be obtained for biochemical analysis. An ultrasound study showed no obstruction nor thrombosis, but signs of prerenal failure. In the first 5 days of treatment there was no clinical response to volumetric expansion and diuretics, thus an obstructive aetiology was suspected. Finally, after several daily ultrasound studies, the accumulation of hypechogenic material obstructing the renal pelvis was detected. Bilateral percutaneous nephrostomy drain tubes were inserted, and intravenous broad-spectrum antibiotic and liposomal amphotericin B (3 mg kg$^{-1}$ per day) were introduced.

At this stage, A. flavus could be identified in samples obtained from the nephrostomy catheters. Sensibility tests based on EUCAST–AFST 2006 guidelines (Lass-Flo¨rl et al., 2006) showed low MICs of amphotericin B (0.5 mg l$^{-1}$), voriconazole (0.5 mg l$^{-1}$), itraconazole (0.25 mg l$^{-1}$) and terbinafine (<0.03 mg l$^{-1}$), but not of caspofungin (>16 mg l$^{-1}$) (Fig. 1).

Serial blood and urine cultures were systematically negative in tests. Thoracic computed tomography, cerebral echography, echocardiography and ophthalmoscopy showed no abnormalities. However, galactomannan antigen blood levels were increased (6.21 ng ml$^{-1}$). At this point, ascending infection with systemic involvement was considered. Amphotericin B urinary tract irrigation at a 50 µg ml$^{-1}$ concentration was applied by nephrostomy catheters three times per day, and treatment with intravenous liposomal amphotericin B was changed to oral voriconazole. Because of the formation of diffuse micro-abscesses in both kidneys and the obstruction of both nephrostomy catheters, we again introduced intravenous liposomal amphotericin B, in addition to oral voriconazole. Three weeks later, the newborn child’s clinical and analytical parameters [including galactomannan antigen levels (3.2 ng ml$^{-1}$)] improved and he could be referred to the ward again.

New renal pelvis obstructions and recurrent urinary tract infection due to Pseudomonas interfered with fungal management. Permanent bilateral ureterostomies were necessary to ensure a correct urine output. After 68 days of systemic combined therapy, itraconazole was introduced instead of voriconazole and liposomal amphotericin B (5 mg kg$^{-1}$ per day in two doses), and antibiotic prophylaxis was instituted. Despite this, galactomannan antigen levels remained stable (3 ng ml$^{-1}$), making an intravenous use of amphotericin B necessary once again until the fungal infection could be partially controlled. Approximately 1 month later the patient was finally discharged.

As of November 2009, the patient was being treated with oral itraconazole and urinary tract infection chemoprophylaxis. He remained carrying bilateral nephrostomies and a ureterostomy. His renal function was conserved and his galactomannan antigen levels remained undetectable. Cellular and humoral immunity, as well as the oxidative capacity of neutrophils, were also normal.

**Discussion**

Despite renal fungus balls having been observed causing anuria in preterm infants in the context of invasive fungal infection, they are still very rare in newborns. Immunosuppression, catheter use and the use of broad-spectrum antibiotics appear to be predisposing factors for fungal infection in preterm infants. Candida spp. is the most common aetiology reported (Vazquez-Tsuji et al., 2005), whereas Aspergillus spp. and other fungi are extremely rare. A. flavus has been identified as a cause of urinary tract infection (Hedayati et al., 2007). Predisposing factors include diabetes, intravenous drug addiction and schistosomiasis (Perez-Arellano et al., 2001). However, according to current medical knowledge, no case of renal aspergillosis in immunocompetent neonates has been reported. The severe urinary tract malformation might have been one factor that fostered the fungus infection, although this theory has not been proved so far.

Ultrasonography is the most effective method for detecting fungus balls (Stuck et al., 1982). Direct microscopic examination of blood and urine samples provides a diagnosis in a relatively short period of time, before the final confirmation by culture. Also, in some cases, it can be the only evidence of fungal infection (Gadea et al., 2007). Due to only a minor effectiveness of cultures to demonstrate fungi in biological samples, serological tests are gaining importance, especially concerning the detection of circulating galactomannan antigen.

There exists little reliable information about the management of renal aspergillosis, especially in paediatric patients, where antifungal therapy for invasive aspergillosis is based on data gathered from the adult population (Blyth et al.,

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**Fig. 1.** Microscope image of sample stained with 1% toluidine blue consistent with a filamentous fungus growing to form sharp angles.
2007). It is recommended to use a combination of systemic antifungal agents, placement of bilateral percutaneous nephrostomy catheters and local irrigation with amphotericin B (Walsh et al., 2008).

When deciding on a systemic antifungal agent in the case of ascending renal aspergillosis and the presence of fungus balls, some aspects should be considered: (a) activity against Aspergillus, (b) nephrotoxicity, (c) distribution in the renal parenchyma and (d) urinary elimination as an active form. Results regarding kidney function have been linked more closely to serum than urine levels. Therefore, concentrations in the renal parenchyma are more relevant than in urine (Andes, 2006). Active agents against Aspergillus spp. (amphotericin B, itraconazole, voriconazole or caspofungin) provide good tissue concentration but are secreted into the urine in a low proportion.

Voriconazole is currently considered superior to amphotericin B, and no nephrotoxicity has been observed. It provides a high concentration in tissues, even if less than 2–5 % is secreted as an active metabolite into the urine. Oral application offers good bioavailability and is preferred in the case of renal failure. Conventional amphotericin B is an additional option, although nephrotoxicity is a limiting factor for its use. Lipid formulations present a worse penetration in renal parenchyma. In our opinion, itraconazole ought to be used in refractory patients, being the most appropriate option to manage renal aspergillosis without systemic involvement. Distribution is better in renal parenchyma and the drug can be secreted into urine in a proportion of 35–40 % as active metabolites. Despite good tissue distribution of echinocandins or posaconazole, lack of experience of their use in pediatric patients precludes their use to refractory cases or cases of intolerance to other antifungal agents. The effectiveness of antifungal combined therapy has not been established yet due to it showing variable results (Steinbach et al., 2003). O’Shaughnessy et al. (2006) found synergy with voriconazole and amphotericin B in low concentrations combined with a wide range of caspofungin concentrations against isolates of Aspergillus fumigatus, A. flavus and Aspergillus terreus.

In our case, the combination of local and systemic amphotericin B with oral voriconazole, followed by oral itraconazole, improved invasive aspergillosis remarkably. However, it did not achieve a complete removal of fungal colonization, most likely due to the severe urinary tract malformation. An important factor for avoiding new episodes of obstruction and reactivation of Aspergillus infection proved to be the management of the urinary tract obstruction with permanent bilateral ostomies and antibiotic prophylaxis.

References


