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Case Report

Primary renal aspergillosis in a newborn: a case report and review of the literature on children

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ABSTRACT

Background. Primary renal aspergillosis is uncommon and mainly affects people with immune system impairment and/or genitourinary disease.

Case. We report the case of a male newborn with Down syndrome and congenital heart disease, who underwent surgery for anorectal malformation and presented persistent fever and impaired kidney function secondary to kidney abscesses due to *Aspergillus*. The patient responded favorably to antifungal treatment and percutaneous drainage but died following heart surgery.

Conclusions. To the best of our knowledge, only seven cases of renal aspergillosis have been reported in children worldwide, this being the second in a newborn. *Aspergillus* species must be considered among the fungal etiological agents of genitourinary tract infections in order to establish adequate antifungal treatment to achieve therapeutic success against filamentous fungi.

Key words: *Aspergillus*, aspergillosis, kidney, child, pediatrics.

Aspergillosis is a major fungal infection in severely immunocompromised adults and children.[1] The estimated annual incidence of aspergillosis is 437 cases/100,000 (0.4%) in high-risk immunocompromised children, including those undergoing allogeneic hematopoietic stem cell transplantation, and children with hematological malignancies such as acute myeloid leukemia or primary immunodeficiencies including chronic granulomatous disease, among others.[1,2]

Aspergillosis is rare in non-immunocompromised children, including neonates and premature infants.[3] It is unusual for *Aspergillus* species to primarily affect extrapulmonary organs, such as the genitourinary tract[4], being secondary to invasive and/or disseminated forms in most cases.[5]

We present a case of primary renal aspergillosis in a newborn without comorbidity of the genitourinary tract and apparently not immunocompromised.

Case Report

A male newborn diagnosed with Down syndrome, congenital heart disease (ventricular septal defect and patent ductus arteriosus), and anorectal malformation without fistula was referred to our institution for surgical management. After surgery for the anorectal malformation, the infant presented severe sepsis, observing the presence of *Acinetobacter iwofii* and *Escherichia coli* in blood cultures. The patient progressed with clinical deterioration and hemodynamic instability, requiring the use of vasopressors, ventilatory support, and broad-spectrum antibiotic treatment with meropenem

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and vancomycin. Although subsequent blood cultures were negative, there was persistence of fever, altered inflammatory markers (C-reactive protein: 74 mg/dl and procalcitonin: 0.7 ng/ml), and an increase in serum creatinine to 0.63 mg/dl. On suspicion of invasive fungal infection, fluconazole was administered for 10 days, and then amphotericin B was continued. Complementary studies including echocardiography, fundoscopy, abdominal ultrasound, and computed tomography urography were performed. The results of echocardiography and fundoscopy showed no evidence of vegetations or signs of fungal endophthalmitis, respectively. Abdominal ultrasound showed altered bilateral renal echogenicity, whereas the tomography showed obstruction of the pelvis and left renal calyces due to renal abscesses (Fig. 1). A left nephrostomy was performed and 15 ml of purulent material was obtained from the drainage of the renal abscesses. Culture with Sabouraud agar showed growth of thick septate hyphae with dichotomous branching compatible with *Aspergillus* spp. Amphotericin B treatment was suspended and voriconazole treatment was started at a dose of 9 mg/kg/dose every 12 hours, with favorable clinical, laboratory, and imaging evolution of the patient (Fig. 2). Urine cultures were always negative; however, urinary sediment before initiating voriconazole treatment showed 50 leukocytes per field, positive leukocyte esterase, and 30 red blood cells per field. These findings normalized 2 weeks after treatment (3 leukocytes per field, negative leukocyte esterase, and 5 red blood cells per field). Additionally, venereal disease research laboratory studies and tests for the diagnosis of human immunodeficiency virus (HIV) and hepatitis B virus were performed, all with negative results. Immunoglobulin levels were within normal limits: IgA 50 mg/dl (value normal: 0-83), IgG 353 mg/dl (value normal: 232-1411), IgM 48 mg/dl (value normal:

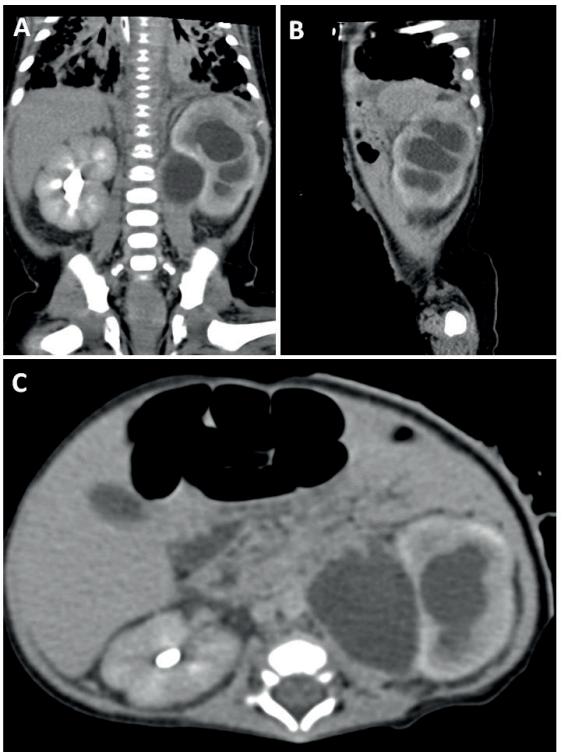

Fig. 1. Computed tomography at the time of diagnosis suggestive of stenosis of the left pyeloureteral junction, which is associated with the presence of renal abscesses.

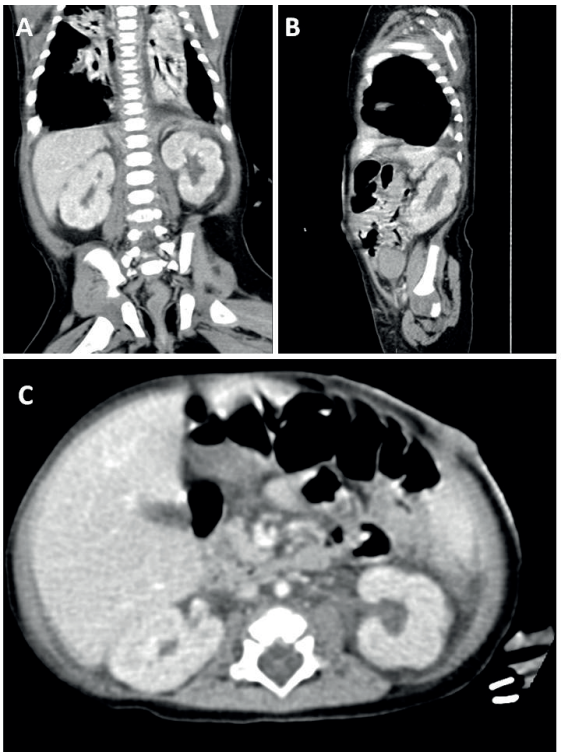

Fig. 2. Computed tomography after drainage of kidney abscesses and specific antifungal therapy, showing evidence of resolution of the findings described.

0-145). The patient completed three months of antifungal treatment and underwent surgery for congenital heart disease using the aorto-pulmonary banding technique plus patent ductus arteriosus closure. The evolution of the patient following surgery was unfavorable, with the presentation of respiratory and hemodynamic deterioration, followed by death.

The case report was approved by the Institutional Review Board of the Instituto Nacional de Salud del Niño San Borja (INSN-SB), under the institutional code PI-257, and that participation involved informed consent.

Discussion

Infection of the genitourinary tract by *Aspergillus* species is an uncommon event that can occur by hematogenous spread in immunosuppressed patients, or by ascending infection from the lower urinary tract.[6] The latter is a rare clinical condition (primary renal aspergillosis), described mainly in adult patients with certain predisposing factors, such as kidney transplantation, HIV infection, diabetes mellitus, obstructive pathology of the genitourinary tract, chronic corticosteroid therapy, use of intravenous drugs, prolonged use of broad-spectrum antibiotics, or the use of invasive devices.[5-9] Including our case, only 7 cases of primary renal aspergillosis have been reported in children worldwide.[9-12] The characteristics of these children are described in Table I. All these cases were male patients, with half being diagnosed with immunodeficiency. Our patient had undergone surgery for anorectal malformation as a comorbid condition similar to the case reported by Martinez-Pajares et al.[9] in a newborn. However, the patient also suffered from bladder exstrophy and epispadias, anatomical alterations of the genitourinary tract that could increase the risk of infection.[13] In addition, Down syndrome, present in our case, has been associated with defects of the immune system such as T and B cell lymphopenia, a decrease of naive lymphocytes, impaired mitogen-induced T cell proliferation, and defects of neutrophil chemotaxis.[14]

The presence of persistent fever and a decrease in the glomerular filtration rate are the main manifestations described in these cases.[15] Urological imaging studies, such as ultrasound or tomography, are important to determine the presence of fungal kidney abscesses or other conditions of the genitourinary tract, which allow establishing an adequate diagnostic and therapeutic plan.[9] Likewise, microbiological identification of the *Aspergillus* species, as well as the performance of antifungal susceptibility tests are crucial to provide targeted antifungal treatment, since antifungal susceptibility patterns differ among the different species.[16,17]

In our report, the culture of the renal abscess was essential to establish the etiological diagnosis. However, it was not possible to perform the antifungal susceptibility test because it was not available at the institution at the time of the present case. In addition to culture, there are

Table I. Characteristics of the seven cases of renal aspergillosis in children reported in the literature.

N° / Year of publication	Age	Sex	Predisposing factor	Location	Aspergilloma
1 / 1977 [10]	6 years	Male	Chronic granulomatous disease	Unilateral	No
2 / 1984 [10]	6 years	Male	Acute lymphoid leukemia	Unilateral	No
3 / 1985 [10]	5 years	Male	Acute lymphoid leukemia	Unilateral	No
4 / 2009 [9]	Newborn	Male	Surgery for anorectal malformation, bladder exstrophy and epispadias	Bilateral	Yes
5 / 2014 [12]	2 years	Male	-	Bilateral	Yes
6 / 2015 [11]	6 years	Male	Burkitt lymphoma	Unilateral	Yes
7 / Present case	Newborn	Male	Surgery for anorectal malformation	Unilateral	Yes

other diagnostic tests for aspergillosis that are based on the detection of components of the fungal cell wall, such as galactomannan (GM). The GM test is primarily useful for the diagnosis of invasive aspergillosis (angioinvasive form) in neutropenic patients.[3,4] However, its sensitivity in non-neutropenic patients is low due to the ability to clear the fungal mannan components mediated by mannosyl macrophage receptors in the bloodstream.[18] Park et al. reported that the serum GM test has a low sensitivity in patients with pulmonary aspergilloma without vascular compromise.[19] Additionally, in children, the presence of false-positive results could be observed due to a cross reaction with lipoteichoic acid from *Bifidobacterium bifidum pennsylvanicum*, a bacterium that is part of the intestinal microbiota, especially in neonates.[3]

Regarding treatment, the guidelines suggest that for the management of renal aspergillosis, as well as in other extrapulmonary aspergillosis, it is important to consider adjuvant surgery (such as ureteral stenting, percutaneous nephrostomy, and even nephrectomy) in addition to antifungal therapy.[17,20] The antifungal therapy of choice in renal aspergillosis is voriconazole. However, although it is used in different age groups in some centers, the use of voriconazole in children under 2 years of age is not authorized and therapeutic drug monitoring should be used to guarantee adequate exposure to the drug.[21] Likewise, if creatinine clearance levels are less than 50 ml/min, intravenous administration should be avoided, due to the possible accumulation of the solubilizing sulfobutyl ether cyclodextrin, which would further affect kidney function.[15] In these cases, one could choose to administer voriconazole orally or switch to another antifungal with a spectrum against *Aspergillus*, such as itraconazole or liposomal amphotericin B.[17,20] In some cases, the use of combined antifungal therapy has even been described.[11] In our case, despite the patient being under 2 years of age and having no results for the antifungal susceptibility test or *Aspergillus* speciation, a favorable response was obtained with voriconazole, observing a decrease in fever, imaging resolution in relation to the presence of kidney abscesses and normalization of urinary sediment (mainly leukocyturia and hematuria), respectively (urine culture was always negative). However, three months after completing the voriconazole treatment, the patient underwent cardiac surgery and died after progressing unfavorably.

In conclusion, although there are few reported cases of primary renal aspergillosis in children, for the diagnosis of primary fungal infections it is important to consider not only yeast fungi, such as Candida species, but also filamentous fungi, such as *Aspergillus*, especially in immunosuppressed children and in those with intra-abdominal malformations (mainly of the genitourinary tract). In addition, we highlight the importance of drainage as a diagnostic and therapeutic method that allows identification of the fungus and the reduction of fungal load. In turn, identification allows establishing a timely and appropriate treatment to achieve therapeutic success.

Ethical approval

The case report was approved by the Institutional Review Board of the Instituto Nacional de Salud del Niño San Borja (INSN-SB), under the institutional code PI-257, and that participation involved informed consent.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: JMA, MLV, JWL; data collection: JMA, MLV, DPA; analysis and interpretation of results: JMA, MLV, JWL; draft manuscript preparation: JMA, MLV, DPA, JWL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Groll AH, Schrey D, Tragiannidis A, Bochennek K, Lehrnbecher T. Invasive aspergillosis in children and adolescents. Curr Pharm Des 2013; 19: 3545-3568. https://doi.org/10.2174/1381612813199990311
2. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics 2006; 117: e711-716. https://doi.org/10.1542/peds.2005-1161
3. Frange P, Bougnoux ME, Lanternier F, et al. An update on pediatric invasive aspergillosis. Med Mal Infect 2015; 45: 189-198. https://doi.org/10.1016/j.medmal.2015.04.006
4. Wattier RL, Ramirez-Avila L. Pediatric invasive aspergillosis. J Fungi (Basel) 2016; 2: 19. https://doi.org/10.3390/jof2020019
5. Ullah SR, Jamshaid A, Zaidi SZ. Renal aspergilloma presenting with pelvi-ureteric junction Obstruction (PUJO). J Pak Med Assoc 2016; 66: 903-904. PMID: 27427147.
6. Najafi N, Shokohi T, Basiri A, et al. Aspergillus terreus-related ureteral obstruction in a diabetic patient. Iran J Kidney Dis 2013; 7: 151-155. PMID: 23485541.
7. Yoon YK, Kang EH, In KH, Kim MJ. Unilateral ureteral obstruction caused by Aspergillus, subgenus Nidulantes in a patient on steroid therapy: a case report and review of the literature. Med Mycol 2010; 48: 647-652. https://doi.org/10.3109/13693780903403035
8. Oosten AW, Sprenger HG, van Leeuwen JTM, Meessen NEL, van Assen S. Bilateral renal aspergillosis in a patient with AIDS: a case report and review of reported cases. AIDS Patient Care STDS 2008; 22: 1-6. https://doi.org/10.1089/apc.2007.0051
9. Martinez-Pajares JD, Martinez-Ferriz MC, Moreno-Perez D, Garcia-Ramirez M, Martin-Carballido S, Blanch-Iribarne P. Management of obstructive renal failure caused by bilateral renal aspergilloma in an immunocompetent newborn. J Med Microbiol 2010; 59: 367-369. https://doi.org/10.1099/jmm.0.012799-0
10. Pérez-Arellano JL, Angel-Moreno A, Belón E, Francès A, Santana OE, Martín-Sánchez AM. Isolated renoureteric aspergilloma due to Aspergillus flavus: case report and review of the literature. J Infect 2001; 42: 163-165. https://doi.org/10.1053/jinf.2000.0786
11. Carlesse F, Marcos ACC, Seber A, et al. Renal aspergillosis in a 6-year-old male with Burkitt's lymphoma. Pediatr Infect Dis J 2015; 34: 679-680. https://doi.org/10.1097/INF.0000000000000696
12. Shohab D, Hussain I, Khawaja A, et al. Primary renal aspergillosis and xanthogranulomatous pyelonephritis in an immuno-competent toddler. J Coll Physicians Surg Pak 2014; 24: S101-S103.
13. Veauthier B, Miller MV. Urinary tract infections in young children and infants: common questions and answers. Am Fam Physician 2020; 102: 278-285.
14. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. Clin Exp Immunol 2011; 164: 9-16. https://doi.org/10.1111/j.1365-2249.2011.04335.x
15. Shannon EM, Reid MJA, Chin-Hong P. Late aspergilloma of a renal allograft without need for operative management: a case report and review of the literature. Transpl Infect Dis 2016; 18: 261-265. https://doi.org/10.1111/tid.12495
16. Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects: two prospective, multicentre, open-label, parallel-group volunteer studies. Clin Drug Investig 2008; 28: 409-420. https://doi.org/10.2165/00044011-200828070-00002
17. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63: e1-60. https://doi.org/10.1093/cid/ciw326
18. Ku NS, Han SH, Choi JY, et al. Diagnostic value of the serum galactomannan assay for invasive aspergillosis: it is less useful in non-haematological patients. Scand J Infect Dis 2012; 44: 600-604. https://doi.org/10.3109/00365548.2012.657672
19. Park SY, Lee SO, Choi SH, et al. Serum and bronchoalveolar lavage fluid galactomannan assays in patients with pulmonary aspergilloma. Clin Infect Dis 2011; 52: e149-152. https://doi.org/10.1093/cid/cir027
20. Garcia-Vidal C, Alastruey-Izquierdo A, Aguilar-Guisado M, et al. Executive summary of clinical practice guideline for the management of invasive diseases caused by Aspergillus: 2018 Update by the GEMICOMED-SEIMC/REIPI. Enferm Infecc Microbiol Clin 2019; 37: 535-541. https://doi.org/10.1016/j.eimc.2018.03.018
21. Ferreras-Antolín L, Sharland M, Warris A. Management of invasive fungal disease in neonates and children. Pediatr Infect Dis J 2019; 38: S2-S6. https://doi.org/10.1097/INF.0000000000002317