Virology & Mycology
ISSN: 2161-0517

Fadel et al., Virol-mycol 2016, 5:3
DOI: 10.4172/2161-0517.1000160

Case Report OMICS International

Localized Renal Graft Aspergillosis in a Child after Kidney Transplantation: Case Report and Review of Literature

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Rec date: Oct 12, 2016; **Acc date:** Nov 09, 2016; **Pub date:** Nov 12, 2016

Abstract

Pediatric kidney transplant recipients are at special risk of infection with opportunistic fungi, such as *Aspergillus* spp., which is uncommon but can be fatal. We report a 16 year male renal transplant recipient, who suffered from acute graft dysfunction five months post transplantation. Imaging of the graft revealed sever back pressure and increased echogenic contents with a distinct pelviureteric ill-defined small mass. Percutaneous nephrostomy was done to relieve the obstruction and microscopic examination and fungal culture of the nephrostomy urine were done which revealed the organism (*Aspergillus fumigatus*). He developed initial improvement subsequent to relief of obstruction; graft function partially regained and received voriconazole for six months. His radiological finding gradually disappeared and graft function resumed to an acceptable level 4 weeks later. As of September 2016 (6 years later), despite the graft injuries, graft function had been conserved. This case serves to reinforce the concept that high index of suspicion of such infection and repeated examination with specific culture media are mandatory for transplant recipients particularly being potentially treatable and if neglected might be fatal infection.

Background

Fungal infections occur in children undergoing each type of Solid Organ Transplantation (SOT), mostly due to Candida spp., with the most likely site of infection being nearest the site of surgery [1]. For kidney transplant recipients; the urinary tract is the most common site [2]. Invasive Aspergillosis (IA) incidence is low in kidney transplant recipients although potentially lethal [3]. The frequency of *Aspergillus* infection in renal transplant recipients is between 0.5% and 2.2% with a mortality rate of more than 88% [4]. Localized renal aspergillosis is by far a rare entity, to which patients with compromised immune status are more vulnerable group [5].

The origin of *Aspergillus* infection in transplant patients, although not well defined in many cases, is usually the immunosuppressed transplant recipient. Transmission from an immunosuppressed and subclinically infected donor has been reported [6,7] although iatrogenic contamination during preservation or perioperatively could not be excluded in the latter case.

Diagnosis of localized primary renal *Aspergillus* infection requires careful investigations due to its benign presentation and lack of associated systemic clinical features. There is also paucity of information on the role of conservative treatment of such localized infection with antifungal agents only [8]. Early diagnosis improves mortality but can be challenging. The introduction of Voriconazole has played a role in decreasing morbidity and mortality, when compared to amphotericin B [9].

Asperigellus fumigatus is an opportunistic pathogen that causes 90% of IA due to Aspergillus genus, with a 50–95% mortality rate, and is one of the most common Aspergillus species to cause disease in individuals with an immunodeficiency and represents a major cause of morbidity and mortality [10].

A few cases of localized renal graft aspergillosis have been reported post kidney transplantation, especially in pediatric population. Here, we describe a case of localized renal graft aspergillosis five months post kidney transplantation, which was successfully treated with Voriconazole.

Case Presentation

A 16 year old male child presented by hematuria followed by anuria and impaired graft function five months post transplantation. Graft ultrasound revealed sever back pressure changes and increased echogenic contents with a distinct pelviureteric ill-defined small mass.

After obtaining an informed consent we will tell the story of the child. He suffered since age of one month when he presented by picture of Chronic Renal Failure (CRF). Imaging of native kidneys revealed a picture suggestive of Autosomal Recessive Polycystic Kidney (ARPKD) and he was managed conservatively. He developed GIT bleeding 3 years later which was explained by having Portal Hypertension (PH) and was controlled on propranolol therapy. He passed to End Stage Renal Disease (ESRD) at age of 5 years, when he started regular Hemodialysis (HD).

He was prepared for kidney transplantation at age of 10 years. His father (who was 42 years at time of transplantation with no medical problems) was the donor. Pre transplantation routine investigations were done (blood groups were A1 +ve {donor} & O+ve {recipient}, tissue typing revealed 2 out of 6 mismatches for B and DR alleles of HLA with negative donor recipient cross match by lymphocytotoxcity). Virology screen was negative for both donor and recipient for HCV, HBV, and HIV. Donor was CMV IgG positive while the recipient was CMV IgG negative for which prophylactic valgancyclovair was given. Left native nephrectomy was done one month before transplantation and right native nephrectomy was done intraoperativly. The operation was uneventful with smooth vascular anastomosis. Cold ischemia time was 70 min with adequate intra and postoperative fluid and electrolyte management. The child received non depleting antibody induction

immunosuppression (basiliximab), maintainace triple therapy protocole (steroids, calcinurine inhibitors & mycophenolate mofetile) and infection prophylaxsis (Perioperative antibiotics, Sulphamethoxazol-Trimethoprim, Nystatin, Valgancyclovair).

He developed delayed graft function (i.e., failure of decline of serum creatinine with inadequate urine output) for 5 weeks post-operative during which HD was established. Graft ultrasound was normal but Doppler revealed increased resistivity index with picture was suggestive of Acute Tubular Necrosis (ATN). Graft biopsy was done day 14 post transplantation (Figure 1); the pathological findings supported the diagnosis of ATN with no evidence of rejection.

The child was re-biopsied 10 days later due to persistently impaired graft function. The later biopsy revealed persistent acute tubular injury, mild interstitial lymphoplasmacytic infiltarte involving about 30% of cortex (i2), scattered tubulitis with up to 4 lymphocyte/tubule (t1) with normal arterioles and peritubular capillaries (i.e., picture of persistent ATN with superimposed border line rejection). He received non-depleting monoclonal antibody (antithymocyte globulin) and pulse methyl prednisone therapy for treatment of rejection. ATN resolved 5 weeks postoperative and adequate graft function was established (serum creatinine declined to 1.2 mg/dL) and he was discharged on his triple immunosuppressive therapy and infection prophylaxis.

Five months post transplantation, the child presented with Urinary Tract Infection (UTI) associated with impaired graft function. He was admitted and received empirical antibiotic and antifungal (Fluconazole) therapy till culture result available. Culture was negative and he developed transient attacks of gross hematuria with normal systemic bleeding profile. He had an attack of oliguria with rising serum creatinine when graft ultrasound revealed moderately sever backpressure changes and Doppler was unremarkable. Urine culture was repeated for bacterial and fungal growth and was negative for both.

He developed an attack of anuria with rapidly rising creatinine up to 9 mg/dL. Urgent ultrasound revealed severe back pressure and increased echogenic contents with a distinct pelviureteric ill-defined small mass (Figure 2). HD started and urgent percutaneous nephrostomy was done to relieve the obstruction. Urine culture was repeated during this period and was still negative.

Nephrostomy tube urine was analyzed under Electron microscopy and revealed uniform, hyaline, septate fungal hyphae with parallel walls having regular dichotomous branching suggestive of *Aspergillus* spp. Culture of nephrostomy tube urine on Sabourad's dextrose agar grew granular, brown - green colonies with a white apron suggestive of *Aspergillus fumigatus*.

The diagnosis of fungal nephropathy was established, and the patient started Voriconazole therapy. The child had initial improvement subsequent to relief of obstruction (serum creatinine reached 3 mg/dL) and he was discharged on ongoing therapy together with oral Voriconazole.

Graft function and sonographic changes slowly improved (i.e., serum creatinine declined to 1.2 mg/dL four weeks later) and Voriconazole was continued for six months. As of September 2016, the child has stable graft function for 6 years after transplantation (creatinine 1.2-1.4 mg/dL) with no significant abnormal sonographic graft findings.

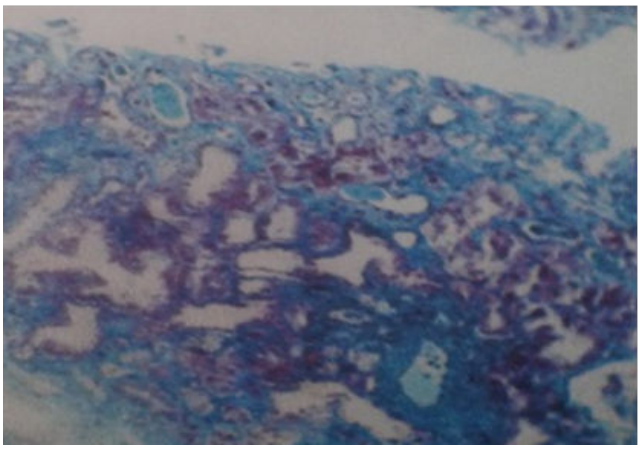

Figure 1: Initial graft Biopsy (Glomeruli: 11 {one is obsolescent} show minimal partial collapse, mild matrix prominence and normal capillary basement membrane.Tubules: mild hydropic degeneration, marked atrophy with collapse and no tubulitis. Interstium: mild fibrosis (5%). Peitubular capillary: normal. Arterioles: thick).

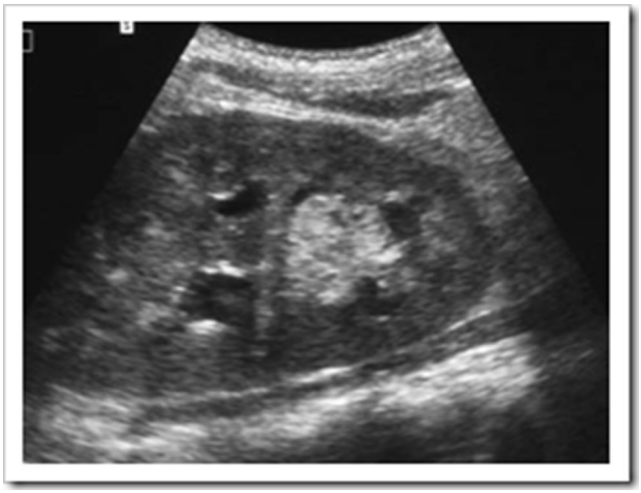

Figure 2: Ultrasound picture of graft pelvis partial obstruction by fungal mass.

Discussion

Infectious complications remain an important cause of morbidity and mortality in children undergoing SOT [1]. In the period from one to six months after transplantation, infections with immunomodulation viruses are most important. In addition; transplant recipients during this period are predisposed to opportunistic infections with organisms as Pneumocystis jiroveci pneumonia, Listeria monocytogenes, and *A. fumigatus* [11]. Our case presented with graft dysfunction due to *Asperigillus* infection five months post transplantation.

Aspergillosis of urinary tract may occur by three ways namely, by ascending infection from the lower tract, from haematogenous dissemination or due to *Aspergillus* cast in renal pelvis. Immunosupression, UT instrumentation and prolonged antibiotic use are major risk factors [14]. Renal aspergillosis due to haematogenous dissemination is the most common while localized infection is rare [12,13].

In our case the infection was a primary and localized aspergillosis of the urinary tract as no other known focus of fungal infection was present elsewhere in the body as that described by Haq et al., who reported a case of primary localized renal asperigellosis in diabetic patient after doing lithotripsy [8]. Haq et al., however, had their case passed fungal ball in the urine. Our child had negative urine cultures for fungal infection despite hematuria which could be explained by vascular invasion of the fungus that caused obstructed the pelvis later on by fungal mass.

Haq et al., owed the infection of their case to instrumentation. They suggested that the *Aspergillus* was introduced into the urinary tract during ureteroscopy and placement of stent in the ureter [8]. In our case, however, the time interval (5 months) between the operation and the clinical presentation doesn`t go with Haq et al., source of infection. Still, instrumental contamination with fungal spores during the operation or even while doing the two graft biopsy procedures postoperative, could be the source of infection in our case if it was latent for a period.

Although asperigellosisis is one of the opportunistic infections that is usually seen in immunocompromised patients, Martinez-Pajares et al., reported a case of obstructive renal failure caused by bilateral renal asperigillomata in immunocompetent newborn [9].

Renal involvement is usually silent if the disease is localized to the cortex of the kidney. In our case, fungal masse filled the pelvis of the graft causing hydronephrosis and later on obstructive anuria, similar to what was previously described by Irby et al., [14]. These masses may be passed in the urine as `balls' [8] which is not the case with our patient. Anuria due to bilateral ureteral obstruction (in no transplanted population) with mycelial clumps, has been also reported [9,15].

Early diagnosis improves mortality [16], however is hampered by lack of reliable serum markers, and, at best, often only a probable diagnosis is reached, rather than proven [17]. Ultrasonography is the most effective method for detecting fungus balls [18].

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 [19]. We didn`t detect the fungus in usual urine sample either by direct examination or by culture which could be explained by the lack of direct opening of the fungal mass to the graft pelvis before causing obstructive anuria.

Diagnosis of our cases was provisionally made upon characteristic songraphic graft finding and was confirmed by fungal culture of the nephrostomy urine sample. Culture of the urine on Sabourad's dextrose agar grew granular, brown–green colonies with a white apron suggestive of *A. fumigatus.*

Sang Wook Lee (2010) reported a similar case of an Aspergilloma mistaken for a pelviureteral stone on non-enhanced CT in a 72 year woman with obstructed single functioning kidney. They discovered that it was a fungal bezoar causing ureteral obstruction by culture of the urine drained from the nephrostomy yielded Enterococcus faecalis [20]. 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 [9].

The management of these challenging infections is a problematic issue. Little reliable information exists in the literature about the management of renal aspergillosis in particularly pediatric patients. Most of the available data were gathered based on adult population studies [21]. It is recommended to use a combination of systemic antifungal agents, placement of bilateral percutaneous nephrostomy catheters and local irrigation with amphotericin B.

In our case HD was established due to graft dysfunction till graft nephrostomy was done. Initial improvement subsequent to relief of obstruction was established and serum creatinine declined to 3 mg/dL.

Patient was discharged with ongoing therapy with oral Voriconazole. Graft function and sonographic changes slowly improved, reaching a serum creatinine of 1.2 four weeks later. Voriconazole was continued in our case for six months later. 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 [9].

Aspergillus infection of the renal allograft is associated with allograft loss, anastomotic complications due to thrombosis and infarctions. Several reports of primary urinary tract aspergillosis in renal transplants have been published [7,22]. Of note, in one of these cases [23], the transplant patient with ureteric obstruction, underwent ureteroscopic resection of the fungal mass (debulking of the bezoar).

Our case was fourtionatly diagnosed early and treated promptly without need for graft nephrectomy. Currently, our child has Stable graft function for 6 years after transplantation (serum creatinine 1.2-1.4 mg/dL).

Localized renal aspergillosis should be suspected in renal transplant recipients with suspicious sonographic findings and confirmatory tests should be done. Negative urine fungal cultures do not always exclude the presence of graft asperiglosis with obstructive fungal mass since it is not always opened to the pelvis with shedding of the fungus to the urethra. Nephrostomy urine had to be tested to confirm or exclude the infection. Surgical debulking or relive of obstructing fungal mass together with systemic Voriconazole is efficient in treatment of localized renal graft Asperigillosis in pediatric renal transplant recipient.

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