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A Case of Capd-Related Cryptococcus Peritonitis after Kidney Transplant Failure

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Abstract

A 80-year-old man with severe atherosclerosis and chronic renal disease related to ischemic nephropathy gradually developed diabetes and uraemia six years after a kidney transplant. Immunosuppression included rapamycin 1 mg qd, mycophenolic acid 500 mg qd and prednisone 2.5 mg qd. When CAPD was started only low dose prednisone was maintained to preserve residual kidney function. Thirty days into CAPD, the patient presented with fever (38.4°C): the abdomen was tender, the PD catheter exit site was healthy, the peritoneal fluid was clear. Chest, abdomen and brain imaging were negative. He had blood (17.340/mm3,) and peritoneal fluid (190/mm3) leucocytosis, CRP was increased at 10.2 mg/dl. Blood, urine and peritoneal effluent cultures were collected and iv. ceftriaxone 2 g qd was administered. Three days later the fever had disappeared but CRP increased to 17.8 mg/dl and peritoneal fluid leukocytes rose to 600/mm3. On day 6 the peritoneal effluent culture grew Cryptococcus Neoformans. Intravenous liposomal Amphotericine B 200 mg/day and Flucytosine 2.5 g/day were administered for 4 weeks, with prompt clinical improvement. The PD catheter was removed, and hemodialysis was started.

Cryptococcal peritonitis is uncommon, with only 15 cases described in peritoneal dialysis (PD) patients out of 61 reported between 1951 and 2012, but infection with the pathogen is a recognized complication of immunosuppression. Diagnosis is often difficult while prompt treatment is required. This potentially severe infection should be considered in any PD patients with clinical signs of culture negative peritonitis and recent or ongoing immunosuppressive therapy.

Keywords: *Peritoneal dialysis; fungal peritonitis; cryptococcus; solid organ transplant patients; failing kidney transplant.*

Introduction

Peritoneal dialysis (PD) is a good treatment option for patients returning to dialysis after kidney transplant failure (1), offering similar survival with hemodialysis in large published analysis (2).

Many authors suggest that patients returning to PD may benefit from continuing some immunosuppression, in order to preserve residual kidney function in the graft (3-7), although infection risk is an important issue.

Time to a first peritonitis episode seems to be longer in new PD patients than in patients returning to PD from previous transplant, although the overall peritonitis rate is similar (8). Cryptococcal peritonitis is un uncommon infection, with a total of 61 cases reported between 1951 and 2012: main underlying clinical conditions included liver cirrhosis and HIV-status/ AIDS. Only 15 cases were described among patients with chronic renal failure treated with peritoneal dialysis (9). Our patient adds a failed renal transplant as an additional cause of this rare infection (3).

Case Report

In March 2016 an 80-year-old man, with history of hypertension, severe coronary vasculopathy, aortic

sub-renal dissected aneurism, was admitted to our Renal Division with symptomatic uremia secondary to a failing renal graft. Ten years before he was diagnosed with chronic renal disease related to bilateral nephrolithiasis and ischemic nephropathy, requiring 22 months of hemodialysis before receiving a kidney transplant in December 2011. Immunosuppression consisted in rapamycin, mycophenolate mofetil and prednisone; clinical course was characterized by many infectious episodes, hypertension of difficult control, distal edemas, insulin dependent diabetes, and progressive worsening of renal function up to CKD stage 4.

At the admission the patient, non adherent to the prescribed immunosuppressive therapy and anuric, was treated with hemodialysis until partial recovery of renal function then, at his request, he underwent to a peritoneal catheter placement. At discharge his creatinine was 3.4 mg/dl, urea 103 mg/dl; treatment consisted in furosemide 500 mg q.d. and low dose of immunosuppression with rapamycin 1 mg q.d, mycophenolic acid 500 mg q.d and prednisone 2.5 mg q.d. PD start was postponed at the patient's request.

One month later the patients developed worsening distal edemas and rapid increase of weight of over 10 kg, needing a prescription of spironolactone 100 mg qd and metolazone 2.5 mg twice a week. In the meanwhile rapamycin and mycophenolic acid were stopped, and only prednisone 2.5 mg/day was maintained.

PD training program was rapidly carried over on May, and his blood pressure stabilized at 190/70 mmHg, his weight at 78 Kg, with daily ultrafiltration of -500ml and (CAPD prescription with 2000 ml 1.36% glucose, 2000 ml 2.27% glucose two times, icodextrin 1000 ml as last exchange); diuresis was about 1000 ml per day.

In June 2016, after thirty days into CAPD, the patient was admitted to our Nephrology Division with fever, dyspnea, bilateral lower leg edema, erythema of the left leg skin. On physical examination the patient was normotensive, there was pulmonary congestion, the abdomen was tender to palpation, Blumberg sign was negative. The PD catheter exit-site was intact, without erythema or exudates, peritoneal fluid was clear. Chest X-ray was negative for pneumonia, there were no signs of deep vein thrombosis at the ecodoppler of the legs. Abdomen ultrasound examination excluded the presence of intrabdominal collections or new finding of the graft. Laboratory studies were not significantly changed from baseline except for leukocytes at 17.340×103/mm3, hemoglobin 10.6 g/dl, CRP 10.2 mg/dl. Leukocytes in peritoneal effluent were 190/mm3 (positivity cut off of 100 /mm3). Culture of blood, urine and peritoneal effluent were performed and patient was started empirically on ceftriaxone 2g/daily, and furosemide 500mg/daily. CAPD was continued with the usual schedule obtaining 1000 ml of ultrafiltration every day.

After 3 days the patient was afebrile, the edema and phlogosis at the left leg were reduced as well as the pulmonary congestion, but a subsequent physical examination revealed signs of balanitis, which had lasted for several days but had not been mentioned before. Blood leukocytes were 12.610×103/mm3, but CRP rose to 17.8 mg/dl, and leukocytes in the peritoneal effluent rose to 600/mm3, with negative culture. Intraperitoneal cefotaxime was substituted for ceftriaxone, and additional laboratory and radiologic exams were asked.

On day 6 of hospitalization our laboratory communicated culture positivity for *Cryptococcus neoformans var. Grubii* in the peritoneal effluent collected at the admission. Serum cryptococcal antigen was negative. Brain and chest computed tomography imaging was negative for disease localization at these sites. Based on in vitro susceptibility of isolate, ceftriaxone was stopped and liposomal amphotericin B 200 mg (3 mg/Kg) daily and flucytosine 2.5g daily (post-dialysis the dialysis day), were started for a 4-week duration, with rapid clinical and biochemical normalization.

On day 8 the PD catheter was removed, and the patient started hemodialysis with a central venous catheter. Blood and urine cultures remained negative throughout his hospital stay. On hospital day 20, he was discharged home, remaining on thrice-weekly hemodialysis.

Discussion

Cryptococcus is an encapsulated yeast found in soil. There are 37 species of Cryptococcus: *Cryptococcus neoformans* and *Cryptococcus gattii* are the major human pathogens (10-12) mainly in immuno compromised patients (13). *C. neoformans* var *grubii* (serotype A) causes most infections in solid organ transplant (SOT) recipients, and is typically a late-occurring infection (14).

Infection is thought to be acquired by inhalation, by the gastrointestinal (GI) tract or the direct blood stream inoculation following upper gastrointestinal bleeding (15-17). Despite being responsible of only 3% of incident cases of invasive fungal infections in SOT recipients, cryptococcosis is associated with a mortality rate of approximately 40% (18).

Chronic graft disfunction, corticosteroids and male gender, as in our patient, are associated with an increased risk of cryptococcosis in SOT recipients (19), while calcineurin-inhibitors (CNI) seem to affect more the severity of cryptococcal disease then the incidence (18).

The main site of infection in SOT recipients is the central nervous system (CNS), accounting for 55% of cryptococcosis (20): in different reports 61% of the SOT recipients had disseminated disease, 54% had pulmonary disease (19). Cutaneous disease accounts up to 17.8% of cryptococcal infections in SOT recipients, with a skin, soft-tissue or osteoarticular involvement: 65.2% of lesions occur in the lower extremities (20). Fungal peritonitis requires rapid peritoneal fluid exchanges to reduce the risk of adhesions, early removal of the catheter and prompt start of parenteral antimycotic treatment with amphotericin B, followed by oral fluconazole, which can achieve a peritoneal penetration of more than 60% (21-22).

Randomized, prospective trials of antifungal treatments devoted to cryptococcosis in SOT recipients or in PD patients are still lacking, but the last IDSA Guidelines recommend induction therapy with AmBisome 4mg/kg/d or Abelcet 5mg/kg/d plus flucytosine 100mg/kg/d for 14 days, followed by a consolidation phase with fluconazole 400–800 mg/d for 8 weeks, and a maintenance or suppression therapy with fluconazole 200–400mg/d for at least 6 months, if the immunosuppressant doses are maintained (21-23).

In our patient, with infection limited to the peritoneal cavity, removal of the catheter and a full 4-week course of therapy with liposomal amphotericin and flucytosine (with dose adjustment to renal function for flucytosine) achieved complete resolution of infection. The potential severity of this infection and its association with immunosuppression require that this pathogen be considered in all PD patients with clinical signs of culture negative peritonitis, and recent or still ongoing immuno suppressive therapy.

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