CLINICAL VIGNETTE

Management of Diffuse Pulmonary Coccidioidomycosis in End Stage Renal Disease

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Case

A 38-year-old Filipino male with a history of end stage renal disease (ESRD) secondary to IgA nephropathy undergoing nightly peritoneal dialysis (PD) presented to an urgent care center complaining of two days of coughing and right sided pleuritic chest pain. He had myalgias, fever, and chills and had taken acetaminophen without improvement. He was seen in PD clinic the day prior with cauterization of a soft tissue growth around the PD catheter site and was empirically started on Ciprofloxacin. He had received the flu vaccine this past year and reports a recent emergency room visit 1 week ago with his ill child. His family had recent viral illness attributed to the flu (though not confirmed) two weeks ago. Mother had positive quantiferon. Father had history of latent TB infection. The patient denies prior fever, night sweats, and weight loss. CXR in urgent care showed a new moderate thickening of the right upper lobe perihilar bronchovascular interstitium and ill-defined perihilar ground glass density suspicious for early bronchopneumonia. Ciprofloxacin was changed to Levofloxacin for presumed Community Acquired Pneumonia. Dose was adjusted for renal failure, 750 mg once and then 500 mg every 48 hours for 4 doses. He presented two days later in the Emergency Room with fevers as high as 102.7 and persistent cough. Repeat chest x-ray demonstrated prominence in the right hilar region, concerning for mass or adenopathy. He received fluids and parenteral vancomycin and piperacillin/tazubactan in the ER and admitted to medicine for sepsis from community acquired pneumonia.

The admitting team was also concerned about other etiologies and obtained fungal cultures, respiratory virus panel and quantiferon gold. Chest CT showed right upper lobe consolidation and ground glass opacities throughout both lungs most consistent with multifocal pneumonia. It also showed "reactive" mediastinal, right hilar and right upper lobar lymphadenopathy. Antimicrobial treatment for Community Acquired Pneumonia was initiated and expanded due to persistent fever of 39.5°C and tachycardia. He also received one dose of fluconazole for fungal coverage along with oseltamivir for possible influenza. On hospital day two, he remained febrile, tachycardic, with WBC of 16 K. Nasopharyngeal swabs returned negative for Flu A/B and respiratory gram stain showed a small number of lactose negative gram negative bacilli. Infectious Diseases recommended Fluconazole 400 mg daily. Fever and leukocytosis persisted despite vancomycin, azithromycin, and fluconazole. On hospital day 5, the fungal respiratory culture grew coccidioides immitis as well as positive Cocci IgM ND, IgM 0.250 and serum complement fixation less than 1:2. Airborne precautions were initiated, antibiotics and fluconazole were discontinued. Amphotericin B Lipid Complex was started for diffuse pulmonary coccidioides.

The patient was clinically worsening with persistent cough, fever, leukocytosis, and increasing oxygen requirements. Lumbar puncture and bone scan were negative for disseminated coccidioides and he remained on amphotericin B with hydration. Skin biopsy of a nodule showed nonspecific eosinophilic infiltration, consistent with an allergic reaction. On day 10 of hospitalization his fever decreased, oxygenation improved and he was changed to oral antifungal coverage with posaconazole. He continued to improve and was discharged on posaconazole after 14 days of hospitalization. Two weeks after discharge, coccidioides antibody titers returned at 1:64 and continued posaconazole was recommended indefinitely. Five months into treatment he developed abdominal pain with elevated amylase and lipase. Due to concern for posaconazole induced pancreatitis, he was switched back to fluconazole, with repeat coccidioides antibody complement fixation level returning less than 1:2.

Discussion

In the southwestern region of the United States, coccidioidomycosis commonly presents as community-acquired pneumonia (CAP). In particular, immune-compromised patients or those with specific risk factors such as Filipino ancestry have a much higher risk of *Coccidioides* infection, and disseminated coccidioidomycosis.[1,2] ESRD has been associated with deficiencies in both humoral and cellular immunity.[1,3] Treatment and management of patients with ESRD present with special challenges, particularly with medication dosing and medication side effects. Our patient with ESRD secondary to IgA-nephropathy, developed severe multifocal pneumonia due to diffuse pulmonary coccidioidomycosis and presented unique treatment challenges.

Immune-competent patients who present with uncomplicated pneumonia do not require antifungal drugs.[1] However, patients with severe pulmonary involvement or additional risk factors are treated with fluconazole or itraconazole at ≥ 400 mg/day for 3-6 months due to increased risk of disseminated coccidioidomycosis.[1,2] Similarly, immunocompromised patients are treated with the same drugs, but for much longer durations (3-6 months or longer).[2]

Treatment guidelines for diffuse pulmonary coccidioidomycosis recommend the use of amphotericin B lipid complex (ABLC) (5 mg/kg/d) or amphotericin B (0.7-1 mg/kg/d) until clinical improvement, followed by fluconazole or itraconazole use for at least another year.[2] Our patient presented with sepsis secondary to a diffuse pulmonary disease with increasing oxygen demand requiring high flow oxygen therapy, was treated with ABLC. Only after stabilization was his treatment changed to fluconazole.

Typically, treatment with fluconazole is preferred over itraconazole due to better absorption and fewer drug interactions.[1] However, for our patient with ESRD, treatment with fluconazole was challenging as fluconazole is mainly excreted through the kidneys. Given that posaconazole, another newer triazole, is not mainly excreted by the kidney and has no major circulating metabolites, the patient was switched to posaconazole 300 mg PO for 6 months after improvement with ABLC.[4]

The most common side effects of posaconazole include diarrhea, headache, fever, hypokalemia, and vomiting. There are also case reports of pancreatitis.[5] Other azoles such as itraconazole, voriconazole, and fluconazole have also been associated with acute pancreatitis rarely.[6-8] Our patient had abdominal pain with elevated lipase and amylase levels, suggestive of acute pancreatitis, and was switched to fluconazole indefinitely. Fluconazole has similar common side effects of nausea, vomiting, and headache.

Risk of dissemination is a major concern when managing patients with diffuse pulmonary coccidioidomycosis. Our patient had greater risk due to ethnic background and immunocompromised state (ESRD). Fortunately, his bone scan, CSF fluid analysis, and skin biopsy were negative for disseminated disease. Disseminated coccidioidomycosis requires a different treatment plan from both primary and diffuse pulmonary coccidioidomycosis, so is critical to diagnose. Treatment for disseminated coccidioidomycosis involves fluconazole or itraconazole administration until clinical improvement and for at least a year following improvement.[2] In severe cases, however, the recommended treatment plan is similar to that of diffuse pulmonary coccidioidomycosis, with amphotericin B followed by fluconazole or itraconazole use for at least another year.[2]

Ultimately, patients with ESRD must be monitored carefully for symptoms of acute pancreatitis and correct dosing based on renal function. This is especially important in the initial treatment of coccidioidomycosis, our patient did not respond to fluconazole, likely to due to incorrect dosing. In addition, the change in the duration of treatment is surprising, given that the patient's initial treatment was for 6 months with posaconazole. Current literature has ambiguous recommendation for treatment duration due to the lack of robust clinical data.[1] The stabilization and laboratory results of the patient serves as the basis of discontinuing treatment.

One of the most widely used diagnostic tools in monitoring the treatment of the patient is the coccidioides complement fixation (CF) titer. Current guidelines suggest monthly coccidioides CF titers for several months, with reduced levels indicating successful treatment.[1,9] Any CF titer level ≤1:4 suggests successful control of *Coccidioides* growth, and if the patient is asymptomatic, can help serve as the basis of discontinuing treatment.[9] Conversely, CF titer levels ≥1:32 suggest possible disseminated coccidioidomycosis and a need for further treatment and testing.[1] In the case of our patient, his CF titer level decreased to 1:2 after 5 months of treatment, suggesting successful control of *Coccidioides*.

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