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Corticosteroids in the Management of Severe Coccidioidomycosis

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TITLE: Corticosteroids in the management of severe coccidioidomycosis

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ABSTRACT:

Introduction: There is limited data suggesting that recovery from severe pulmonary infection with *Coccidioides* may be hastened by the addition of systemic corticosteroids.

Methods/Results: We report two patients with persistent and progressive coccidioidomycosis who demonstrated a dramatic response to adjunctive corticosteroid therapy. Both patients had *Coccidioides immiitis* cultured from respiratory samples. One was a 69 year old man who had been treated with combination fluconazole and liposomal amphotericin for over six weeks, with persistent fever and pneumonia. The other was a 61 year old man treated with fluconazole and then amphotericin for three weeks, with progression to acute respiratory distress syndrome (ARDS) and shock. Both received short courses of intravenous methylprednisolone and recovered to be discharged home.

Conclusion: As opposed to associated hypersensitivity, corticosteroid treatment in these cases was directed at modulating the ongoing destructive effects of unchecked inflammation. Rapid improvement was noted in both cases and raises the possibility that the addition of systemic corticosteroids may hasten recovery in patients with severe coccidioidomycosis.

INTRODUCTION: Coccidioidomycosis can be slow to resolve despite appropriate anti-fungal therapy. Corticosteroids are generally avoided due to concern for further immunosuppression and uninhibited infection. However, recovery from severe coccidioidomycosis may be facilitated by systemic corticosteroids (1). This is a little recognized option for treatment with limited reports in the literature. We report a case series of two patients with severe coccidioidal pneumonia whose recovery was facilitated by systemic corticosteroids.

CASE PRESENTATIONS

Case 1

A 69 year old man, of American Indian heritage, with a distant and minimal smoking history, and diabetes mellitus (HgbA1c 6.8%) was admitted to an outside hospital with a severe left lower lobe (LLL) pneumonia. He developed respiratory failure and was intubated on hospital day (HD) 4. Coccidioidomycosis was diagnosed based on positive IgM titers and growth of *Coccidioides immitis* from bronchoscopy. He started high dose fluconazole (800 mg/d) and liposomal amphotericin (475 mg/d) with subsequent anuric renal failure (attributed to sepsis and contrast nephropathy). Lumbar puncture and brain MRI were negative. He underwent tracheostomy and gastrostomy tube placement and was transferred to our hospital on HD 30. A bone scan was negative for disseminated disease. He completed 28 days of liposomal amphotericin, and continued with high dose fluconazole. There was slow recovery of renal function and dialysis was able to be discontinued on HD 38, but continued with daily fevers (T = 100.0-101.0^{o} F) more than a month after initiation of anti-fungal therapy. He also had an initial eosinophilia (WBC = 4.62 K; Eos 320 or 6.7%) which was persistent and rose to a peak of WBC 5.46 K, eos 630, 11.5% on HD 46). Chest computed tomography (CT) imaging demonstrated densely consolidated lung and modest pleural effusion (Figure 1). Thoracentesis on HD 46 revealed a lymphocytic, exudative effusion with negative cultures. Indwelling intravascular catheters were removed, but his fevers

persisted. He was transitioned to trach collar oxygen, but remained weak and poorly functional with evidence of critical illness polyneuropathy. *Coccidioides* continued to be isolated from sputum. No other site or source of infection was identified despite an extensive search. Given his persistent infection and ongoing systemic symptoms, including fever and eosinophilia, a decision was made on HD 48 to start intravenous methylprednisolone (40 mg/d decreasing 10 mg every three days to complete a 12 day course). He quickly defervesced, demonstrating radiographic and functional improvement. He was transferred to a medical ward on HD 54, improved with physical therapy and rehabilitation, and was discharged to a nursing home. He was eventually discharged home two months later where he has remained, now more than two years after treatment.

Case 2

A 61 year old African American man, distant ex-smoker with hypertension, untreated diabetes mellitus (Hgb A1c 6.8%) and chronic kidney disease was admitted with progression of a LLL pneumonia which had worsened despite a course of doxycycline. Chest CT imaging demonstrated dense consolidation of the LLL and lingula as well as smaller areas of consolidation in all other lobes of the lungs with left greater than right pleural effusions and bulky mediastinal lymphadenopathy (Figure 2). Bronchoscopy was performed during HD 3 and was he was diagnosed with coccidioidomycosis based on positive IgM titers and growth of *Coccidioides immitis* from his bronchoalveolar lavage. He was started on fluconazole (400 mg/d) during HD 3. Head CT was unremarkable and lumbar puncture did not show signs of disseminated disease. He failed to improve and had continued low grade fevers (T = 100.5° F), increasing infiltrates and hypoxemia with hypoxemic respiratory failure requiring intubation on HD 19. He was started on liposomal amphothericin B (280 mg; 5mg/kg), but developed renal failure and hemodialysis was started during HD 20. His respiratory status worsened and he was started on empiric bacterial antibiotic coverage. Initial eosinophil counts of 100 had increased to 500 (2.5%), with a total WBC of 17.8 K. His

respiratory failure progressed to acute respiratory distress syndrome (ARDS) with an arterial blood gas on FIO_2 = 1.0 (7.18/$PaCO_2$ 61 mm Hg/PaO_2 67 mm Hg). He was febrile to 101.5° F and hypotensive on a norepinephrine infusion up to 37.5 mcgm/min. Given his multiorgan system dysfunction and tenuous status, methylprednisolone 60 mg IV Q 6 hrs was started on HD 22. By HD 24 he had a remarkable improvement with decreasing oxygen requirements with an arterial blood gas on FIO_2 = 0.65; (pH 7.41/$PaCO_2$ 40 mm Hg/PaO_2 88 mm Hg). Methylprednisolone was stopped on HD 26 given increasing hyperglycemia and concern for a possible superinfection with multidrug resistant Pseudomonas that had been isolated from respiratory cultures. He continued to improve and was extubated on HD 35. He had remarkable improvement in his renal function and hemodialysis was stopped on HD 37. On HD 42 his liposomal amphothericin B was changed to fluconazole, which he continued for 6 months after discharge. A bone scan did not show signs of disseminated disease. He was transferred to acute rehabilitation and was discharged home on HD 74. He remains functional without any respiratory limitation more than five years since his hospitalization. He had recent pulmonary function tests with normal spirometry and lung volumes and only an isolated diffusing capacity (64%) noted.

DISCUSSION:

Coccidioidomycosis is a fungal infection that has a wide spectrum of manifestations, but most commonly causes a self-limited upper respiratory tract infection in endemic areas (2). Patients with primary pulmonary coccidioidomycosis generally develop a flu like syndrome with cough and fever. It most commonly manifests as lobar or segmental pneumonia with hilar adenopathy. Pulmonary coccidioidomycosis rarely progresses to ARDS, in which mortality may approach 100%. In immunocompetent individuals, severe disseminated disease is rare with an incidence of less than 1%. Eosinophilia is noted on white blood cell differential of peripheral blood in 25-30% of cases. This feature may be helpful on differentiating cocci pneumonia from a bacterial pneumonia (3).

Corticosteroids are also a risk factor for coccidioidomycosis and therefore their use in infected patients is controversial (4). Corticosteroids have been reported as adjunct therapy in coccidioidomycosis, but the rationale has primarily been to treat associated symptoms such as arthralgias or rash. In 1956 Levan et al. published a case series of 19 patients with erythema nodosum or multiforme secondary to primary coccidioidomycosis infection (5). All patients received 25 mg of cortisone orally with total doses ranging between 350 mg and 775 mg administered in a 4-6 day period. All the patients demonstrated immediate resolution of symptoms within 48 hours with improvement of cutaneous lesions and joint swelling within 1-2 days. No antifungal treatment was given to these patients and none of these patients develop disseminated disease. Azadeh et. al. performed a retrospective review of immunocompetent patients with acute pulmonary coccidioidomycosis who received systemic corticosteroids for relief of coccidioidal related symptoms (rash, arthralgia, arthritis) (6). They found no adverse effects of short-term corticosteroid therapy for early symptomatic treatment in acute pulmonary coccidioidomycosis. However, they also found no difference in the duration of symptoms and pulmonary outcomes. The vast majority of these patients also received antifungal therapy.

In addition to peripheral eosinophilia, tissue eosinophilia has been reported in acute coccidioidomycosis and has been seen to increase in advanced cases of coccidioidomycosis (7). This has often been attributed as a hypersensitivity reaction to coccidioidomycosis and reports can be found suggesting that acute eosinophilic pneumonia in coccidioidomycosis or primary coccidioidal pleural effusions are also hypersensitivity reactions that can be treated with corticosteroids (8-9).

However, these previous applications of corticosteroid use differ from the intent described in our cases.

The premise for the use in our cases was to decrease the detrimental effects of the inflammatory response, anticipating that the benefits of treatment outweigh the risks of infection associated with systemic use (10). It is well documented that corticosteroids as an adjuvant treatment for Pneumocystis jiroveci pneumonia have a beneficial effect on mortality and need for mechanical ventilation in patients with HIV infection. A reduction in relative risk of death of 44% at one month and 41% at three to four months was noted in a recent Cochrane review (11). It is the experience with suppression of the inflammatory response associated with treatment of Pneumocystis that has raised the possibility of adding adjuvant corticosteroid therapy in patients with pulmonary coccidioidomycosis and respiratory failure who do not improve despite antifungal treatment.

Our patients are similar to the patient described by Shibli and others (1) who was also treated with corticosteroids after progressing despite over two weeks of antifungal therapy. Both of our patients presented with respiratory compromise and failure to respond to antifungal therapy despite a prolonged treatment course. It is noted that there may have been other confounding issues associated with their response. Both had diabetes mellitus and were from ethnic groups associated with more adverse outcomes in coccidioidomycosis. The previously reported patient was also African-American. One of our patients was treated for over six weeks with appropriate anti-fungal therapy and still had significant systemic symptoms including fever and peripheral eosinophilia. The other had demonstrated progressive decline after starting treatment and was in septic shock with multiorgan system failure including ARDS. The decisions to initiate therapy were carefully weighed against their risks of ongoing decline and death. Of note, both patients had some degree of peripheral eosinophilia and in these patients on adequate therapy, a feature that may represent an indirect marker of progressive disease. Peripheral eosinophilia is also seen in other conditions such as asthma and chronic obstructive pulmonary disease, and has been used as a marker to presage response to corticosteroid therapy. Persistent or increasing peripheral

eosinophilia may be a marker of progression in disease in coccidioidomycosis or persistent inflammation, and therefore a potential marker of corticosteroid responsiveness. This may be helpful in future cases where there is consideration for corticosteroid use, but uncertainty given other co-morbidities and concern for superinfection as in our cases.

CONCLUSIONS: Systemic corticosteroids can enhance recovery in patients with severe coccidioidal pneumonia and the benefits may occur even after several weeks of anti-fungal therapy. The optimal dosing and duration of therapy are not established and is not addressed in the latest guideline on the management of coccidioidomycosis (2). Peripheral eosinophilia may be an indicator of responsiveness to the addition of corticosteroid therapy. Corticosteroids should be considered as an option for patients with severe persistent coccidioidal pneumonia not responding to anti-fungal therapy, however a definitive conclusion will require prospective studies.

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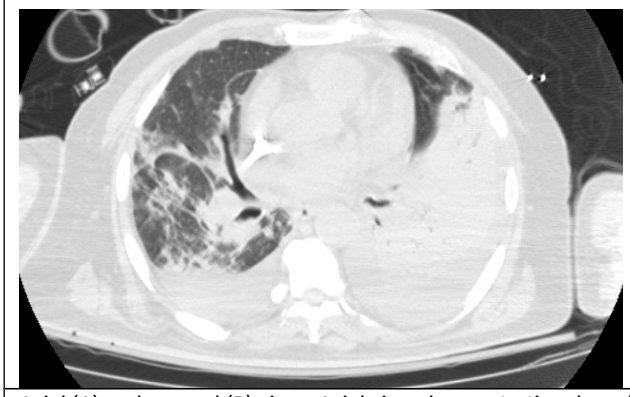
Figure 1. Case 1:

a.



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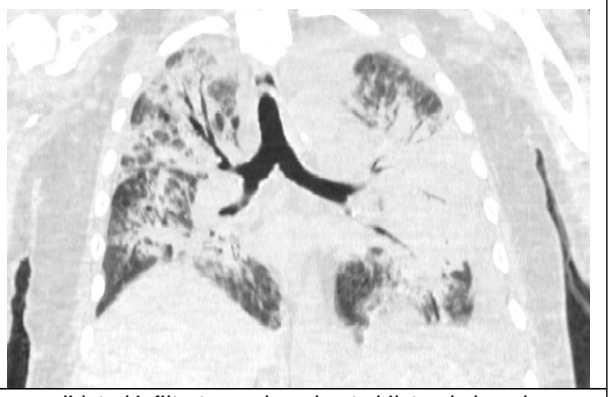
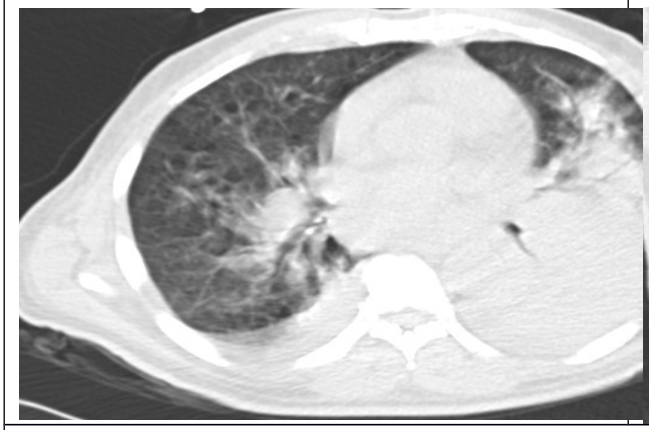


Axial (A) and coronal (B) views Axial view demonstrating densely consolidated infiltrates and moderate bilateral pleural effusions

Figure 2. Case 2:

A.



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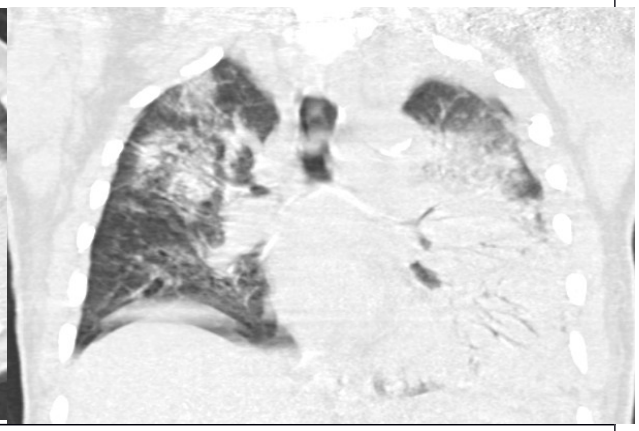

Axia (A) and coronal (B) views demonstrating dense consolidation of the left lower lobe and lingula and smaller consolidations in all other lobes of the lungs with left greated than right pleural effusion.