Proof *Coccidioides* Infections Can Cause Sarcoidosis

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Abstract

Clinical observations on patients who simultaneously had two different granulomatous diseases, both sarcoidosis and coccidioidomycosis, led to the hypothesis for this Scholarly Project – can sarcoidosis be caused by an infection due to the fungus *Coccidioides*? We present epidemiological and clinical evidence as proof that *Coccidioides* can cause sarcoidosis. Based on our findings we propose that sarcoidosis is the result of a cell mediated immune response to *Coccidioides* generated by certain immunologically unique individuals capable of causing what we call "tuberculoid coccidioidomycosis" or sarcoidosis.

Introduction

Sarcoidosis is a disease described over one hundred years ago (1877). To date, the cause is unknown, despite numerous studies. The diagnosis of sarcoid requires finding non-caseating granulomas on tissue histopathology and excluding other etiologic agents. The use of corticosteroids in sarcoid tends to make the disease better.

Coccidioides is a fungus endemic to the Southwestern United States which causes coccidioidomycosis (coccy). It primarily causes pulmonary infections that can present with bilateral hilar adenopathy similar to that seen in the disease sarcoidosis (sarcoid). Like sarcoid, coccy is associated with a granulomatous response, but in contrast to sarcoid, fungal organisms can be seen on histopathology and serologic testing can confirm the diagnosis. The use of corticosteroids in coccy usually tends to make the infection worse.

Study Hypothesis: In patients who have both sarcoid and coccy there are two potential mechanisms for the fungal infection to express itself: 1) the patient has sarcoid, receives immunosuppression (i.e., steroids), then experiences an exposure to *Coccidioides* and develops coccy. An alternative possibility is: 2) the patient has an exposure to *Coccidioides* which manifests itself as sarcoid without any evidence of coccy. Based on the latter hypothesis we report two patients who confirm a clinical and epidemiologic association between coccy and sarcoid.

Methods

1. A medical chart review was conducted at Maricopa Medical Center on all patients with a diagnosis of sarcoidosis between 2004 and 2014 to assess for a potential relationship to *Coccidioides*.
2. A case control study was performed to compare the number of patients with coccy in matched patients with and without sarcoid.
3. Two patients with both coccy and sarcoid were studied, one prospectively and the other retrospectively and their clinical courses were documented.
4. A PCR analysis for *Coccidioides* DNA was carried out on tissue specimens obtained from patients when they were diagnosed with sarcoidosis. If our hypothesis is correct we should be able to identify the presence of *Coccidioides* DNA. (The results of these studies are in progress).

Results

1. Medical chart review identified 4 patients with coccy in the 68 patients identified with sarcoid.
2. A medical chart review was done on a control group of patients matched for age, sex and year of admission for the 68 sarcoid patients. There were 2 patients with coccy in the control group compared to the 4 coccy patients in the sarcoid group. There were more cases of coccy in the sarcoid group, but the difference was not statistically significant, p value < 0.05.
3. Epidemiologic Studies

Prospective Evidence: Case One: A 50 year old white male was diagnosed with sarcoid in 2000 when he had hypercalcemia and underwent a splenectomy for thrombocytopenia. There was no history or laboratory evidence for coccy at the time of the sarcoid diagnosis. His eight year clinical course is shown on Table 1. Postoperatively in 2001 he was started on steroids and followed as an outpatient. Approximately 6 months after his sarcoid diagnosis the patient's *Coccidioides* complement fixation (CF) titer seroconverted from negative to positive at 1:8. Despite the seroconversion he was improving and completely asymptomatic. However, he was empirically placed on fluconazole. Clinically the sarcoid improved and the patient was taken off steroids and fluconazole. After that his coccy CF titer fell to 1:2. Steroids were restarted in June 2002 for polyarticular arthritis and continued until December 2003. During that time, while he was on steroids, his coccy CF titers reached their highest titer of 1:32. Titers ≥ 1:32 are usually associated with patients with disseminated coccy. When the arthritis resolved, the steroids were discontinued and his coccy CF titer fell to 1:4. The patient remained asymptomatic for sarcoid or coccy from June, 2004 to June, 2008 when he presented with swelling of his right sternoclavicular joint. Aspiration of the joint grew *Coccidioides* on culture. He was placed on oral fluconazole which appeared to control the coccy. From June, 2008 to September, 2009 he was able to return to work and his coccy CF titer decreased from 1:8 to 1:2. The patient unexpectedly expired in December, 2009 of "brain cancer".

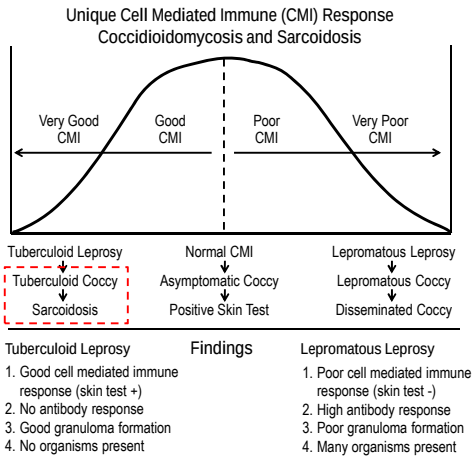
Retrospective Evidence: Case Two: A 34 year old black male was diagnosed with disseminated coccy in 2009 after presenting with fevers, weight loss, malaise and swelling of his left elbow. Cultures of an aspirate from his elbow grew *Coccidioides*; a coccy CF titer at the time was positive at 1:8. He was started on oral fluconazole but had a stormy course despite compliance with therapy. He was treated initially with oral fluconazole, but was changed to voriconazole and then started on intravenous amphotericin B as an outpatient over the years 2009 to 2012. The patient claimed to be compliant over those years, but he never felt the infection was controlled. Despite the antifungal therapy he was hospitalized in 2012 for fevers and respiratory failure which required intubation and mechanical ventilation. A lung biopsy was done which showed non-caseating granulomas consistent with sarcoid. No organisms were seen on histopathology and cultures for *Coccidioides* were negative. Remarkably his coccy CF titers had become negative. There was no evidence of coccy at the time he was diagnosed as having sarcoid.

Table 1. Clinical Course Case One

Date	Clinical Observations	Coccy CF*	ACE**
11/00	Splenomegaly and hypercalcemia	Neg	37
12/00	Splenectomy; DX – sarcoid		
01/01	Started steroids		
03/01	Transient eosinophilia (10%)	Neg	-
06/01	Asymptomatic – started fluconazole	1:8 – IgM+	83
08/01	Asymptomatic	1:8	-
10/01	Asymptomatic – stopped steroids	1:16	-
12/01	Asymptomatic – stopped fluconazole	1:4	108
03/02	Asymptomatic	1:2	-
06/02	Arthritis – had been started on steroids	1:32	44
08/02	Arthritis	1:32	63
10/02	Arthritis	1:32	75
05/03	Arthritis	1:32	109 ←
12/03	Arthritis resolved – stopped steroids	1:32	90
06/04	Asymptomatic	1:32	84
01/05	Asymptomatic	1:16	89
08/05	Asymptomatic	1:8	61
03/06	Asymptomatic	1:4	-
10/06	Asymptomatic	1:16	54
12/06	Melanoma diagnosed	1:8	70
04/07	Asymptomatic	1:8	73
12/07	Asymptomatic	1:8	-
06/08	*Coccidioides* recovered on culture from the sternoclavicular joint – started fluconazole	1:8	-
12/08	Coccy controlled	1:8	52
05/09	Coccy controlled	1:8	-
09/09	Coccy controlled	1:2 – IgM+	-
12/09	Expired "brain cancer"		

* Complement fixation titer to *Coccidioides* (normal = negative)
** Angiotension-converting enzyme level (normal 9-67)

Figure 1. Prototypical Cell Mediated Immune Response as Seen in Leprosy



Discussion

To explain the clinical and epidemiologic observations in our two patients with sarcoid we have hypothesized that sarcoid is due to a unique human immunologic response to *Coccidioides*. Figure 1 illustrates a bell shaped curve that represents the proto-typical human cell-mediated immune response (CMI) observed in leprosy. In Figure 1 we have substituted *Coccidioides* for leprosy to illustrate the range of the CMI responses that can occur with a *Coccidioides* infection. We believe the CMI response to coccy in these two case reports is similar to what would be seen in patients with tuberculoid leprosy. In tuberculoid leprosy the CMI is characterized by good granuloma formation, no organisms are present and there is no detectable antibody response to the leprosy organism. These are the findings seen in sarcoid. We believe our two patients had the equivalent of the CMI response which we call "tuberculoid coccy" [tuberculoid leprosy] where the reaction to the *Coccidioides* infection is immunologically manifest as sarcoid. In contrast, the population with poor CMI are those individuals who develop disseminated coccy and receive all the clinical attention. Those unique individuals that have a "strong" tuberculoid CMI response are immunologically capable of developing a granulomatous "sarcoid" response to a *Coccidioides* infection with no evidence of organisms being present.

Conclusion

To explain why sarcoid appears in areas where there is no *Coccidioides*, we propose it is the immune response to certain other agents, like the systemic fungi, which stimulate the sarcoid response in the immunologically appropriate individuals. So in the mid-west where histoplasmosis is endemic, *Histoplasma capsulatum* would be a cause of sarcoid. These observations explain why multiple agents have been implicated in sarcoid, but never proven. It is not a single agent, but a unique CMI response to a variety of systemic fungi (and probably other agents) which, in our patients, resulted in the "tuberculoid" immune response to *Coccidioides*.