Fungal infections as a complication of therapy for sarcoidosis

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Summary

Background: Treatment of symptomatic sarcoidosis usually includes systemic immunosuppressive agents. These agents may render the patient more susceptible to opportunistic infections. In addition, the fungal infection may be difficult to distinguish from the underlying sarcoidosis.

Aim: To examine the presentation and management of invasive fungal infections in sarcoidosis patients.

Design: Retrospective record review.

Methods: We reviewed the notes of all sarcoidosis patients (n=753) seen at our clinic over an 18-month period.

Results: Seven patients (0.9%) with previously diagnosed sarcoidosis developed fungal infections: two each with Histoplasma capsulatum and Blastomyces dermatitidis and three others with Cryptococcus neoformans. No cases of invasive aspergillus or tuberculosis were identified. The diagnosis of fungal infection was made by bronchoscopy (four cases), open-lung biopsy (one case), bone-marrow aspirate (one case), and spinal fluid examination (one case). All patients were receiving corticosteroids at the time of worsening chest X-ray or clinical status. Four patients were also receiving methotrexate prior to infection. No patient with systemic fungal infection was receiving either infliximab or cyclophosphamide. All patients responded to anti-fungal therapy and a reduction in immunosuppression.

Discussion: Fungal infections occur rarely in treated patients with sarcoidosis. Deterioration of chest X-ray, especially a localized infiltrate, warrants investigation.

Introduction

Corticosteroid therapy has been the standard of care of patients with sarcoidosis since the 1950s. The benefit of glucocorticoids for sarcoidosis has been supported by an evidence-based review of the literature. Additional agents recommended to treat symptomatic sarcoidosis include cytotoxic drugs such as methotrexate and azathioprine. Currently, a wide variety of immunosuppressive drugs have also been proposed as possible agents.

The use of immunosuppressive drugs is associated with an increased risk for infection, especially in the lung. These infections include deep-seated fungal pathogens such as Histoplasma capsulatum, Blastomyces dermatitidis, and Cryptococcus neoformans. In addition, Apergillus can form mycetoma and become invasive. Other opportunistic infections include Mycobacteria tuberculosis. In addition to these infections being associated with immunosuppression, all these infections have occurred in patients with sarcoidosis.

Fungal or tuberculous infections can produce a sarcoid-like reaction to the infectious agent. Fungal or tuberculous infections can produce a sarcoid-like reaction to the infectious agent.
Methods

All patients seen at the Interstitial Lung Disease and Sarcoidosis Clinic over an 18-month period were entered into a database, and the records of all patients with sarcoidosis during that time were reviewed. Information entered into the database includes the primary diagnosis, secondary diagnosis including infections, therapy, and outcome. The study was approved by the University of Cincinnati Institutional Review Board.

Patients with fungal infection diagnosed during that time were specifically evaluated to ascertain that they had a biopsy-confirmed diagnosis of sarcoidosis and a clinical presentation that met the ATS/ERS/WASOG criteria for diagnosis\(^3\) at least one year prior to being diagnosed with infection.

In addition to the immunosuppressive therapy at time of fungal infection, the treatment and clinical responses of all patients with fungal infection were noted. Information including all immunosuppressive therapy for those patients who did not have fungal infection was also reviewed.

Results

In total, 753 sarcoidosis patients were seen over the 18-month period. Data were analysed from a total of 3466 clinic visits, with some 4–5 clinic visits per patient.

During the study, 645 patients received treatment; 108 (14%) remained untreated (Table 1). We noted those patients who during the time period received only prednisone, only methotrexate, or both agents. The use of additional agents either alone or in combination is also shown in Table 1. The patients who developed fungal infections were receiving prednisone with or without methotrexate.

Seven invasive fungal infections were diagnosed during the 18 months of the study: pneumonia only (\(n = 4\)), pneumonia and disseminated infection (\(n = 2\)), and meningitis (\(n = 1\)) (Table 2). Although no cases of invasive aspergillus were diagnosed during the study period, seven patients were diagnosed with non-invasive aspergillomas during the study period.

Two patients developed disseminated histoplasmosis while on therapy for their sarcoidosis. Therapy for sarcoidosis prior to fungal infection included prednisone (\(n = 2\)) and methotrexate (\(n = 1\)). Both developed increasing dyspnoea with diffuse pulmonary infiltrates (Figure 1A). Corticosteroid dosage was initially increased, as the treating physician felt the infiltrates represented worsening sarcoidosis. The patients underwent evaluation for infection when they developed hepatic dysfunction and evidence for disseminated intravascular coagulopathy, with markedly elevated D-dimer. In one patient, a bronchoalveolar lavage sample grew *H. capsulatum*. In the other, a bone marrow biopsy demonstrated fungal elements in the bone marrow, and cultures were positive for *H. capsulatum*. The patients experienced resolution of their lung infiltrates with amphotericin B initially, followed by a switch to an oral azole (Figure 1B) for one year. Currently, they remain on low-dose prednisone to treat their sarcoidosis and no further anti fungal therapy.

The immunosuppressive therapy prior to diagnosis of infection is shown in Table 3. In all seven

<table>
<thead>
<tr>
<th>Fungal infection</th>
<th>Cases</th>
<th>Method of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated histoplasmosis</td>
<td>2</td>
<td>Bronchoscopy 1, bone-marrow aspirate 1</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>1</td>
<td>Spinal fluid</td>
</tr>
<tr>
<td>Pulmonary cryptococcosis</td>
<td>2</td>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>Pulmonary blastomycosis</td>
<td>2</td>
<td>Bronchoscopy 1, open lung 1</td>
</tr>
</tbody>
</table>

Table 2 Fungal infections encountered

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients treated</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone without methotrexate</td>
<td>235</td>
<td>3</td>
</tr>
<tr>
<td>Prednisone plus methotrexate at any time*</td>
<td>214</td>
<td>4</td>
</tr>
<tr>
<td>Methotrexate without prednisone</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>Additional therapy**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>187</td>
<td>0</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>117</td>
<td>0</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>No therapy</td>
<td>108</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are numbers. *Patients who were on prednisone and methotrexate together at any time during the observation period. **Patients could be on one or more drugs alone, or in combination with prednisone or methotrexate.
cases, patients had received glucocorticoids for more than a year prior to diagnosis of infection. In four patients who received methotrexate, treatment at time of infection ranged from 4 to 24 months (median 6 months) and the median prednisone dose at time of diagnosis was 20 mg (range 10–40 mg/day). After the diagnosis of fungal infection, corticosteroid dosage was reduced to a median of 5 mg/day (range 0–10 mg/day).

Patients received at least one year of azole antifungal therapy. In four cases, anti-fungal therapy was discontinued after one year. This included the two cases with histoplasmosis and two cases of blastomycosis. One patient had no evidence of fungal infection and had stable (Stage 2) sarcoidosis remained on prednisone 10 mg/day and hydroxychloroquine 400 mg/day. His chest X-ray remained stable for more than 6 months and

Table 3  Treatment for patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Fungus</th>
<th>Initial sarcoidosis therapy</th>
<th>Anti-fungal therapy</th>
<th>Current therapy for sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Histoplasmosis</td>
<td>Prednisone</td>
<td>Amphotericin</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>2</td>
<td>Histoplasmosis</td>
<td>Prednisone</td>
<td>Amphotericin</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>Itraconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>3</td>
<td>Cryptococcosis</td>
<td>Prednisone</td>
<td>Amphotericin</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>Fluconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>4</td>
<td>Cryptococcosis</td>
<td>Prednisone</td>
<td>Amphotericin</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>Voriconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>5</td>
<td>Cryptococcosis</td>
<td>Prednisone</td>
<td>Fluconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>6</td>
<td>Blastomycosis</td>
<td>Prednisone</td>
<td>Itraconazole</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td>7</td>
<td>Blastomycosis</td>
<td>Prednisone</td>
<td>Itraconazole</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

\[Figures and tables inserted here\]

Figure 1. Patient with sarcoidosis received prednisone 20 mg/day and methotrexate 10 mg/week, and developed worsening chest symptoms. Chest X-ray (A) revealed diffuse infiltrates. *Histoplasmosis capsulatum* was cultured from bronchoalveolar lavage fluid. Patient was treated with amphotericin followed by itraconazole. Methotrexate was discontinued and prednisone was reduced to 5 mg/day. Chest X-ray shows resolution of pulmonary infiltrates (B).
he reported no pulmonary symptoms. However, within 3 months of stopping itraconazole, he developed increasing cough, dyspnoea, fatigue, and low-grade fever. His chest CT scan demonstrated new patchy infiltrates, some in areas of prior calcification (Figure 2). The bronchoalveolar lavage culture grew *B. dermatitidis*. Within 2 months of being restarted on itraconazole, his symptoms resolved.

**Discussion**

Immunosuppressive therapy is recommended for symptomatic sarcoidosis.3 Because the patient can relapse when the drug is withdrawn,16 these agents are often used for prolonged periods. All patients followed in the clinic were seen by either one of the two authors. We specifically recorded the information regarding infections during the 18-month observation time. This information was subsequently retrieved from the computer database used in our clinic. Invasive fungal infections were reported in 7/753 patients during the 18 months of the study. Four of the patients were infected with fungi endemic to our area: *H. capsulatum* and *B. dermatitidis*. It is possible that we missed some opportunistic infections in these patients. However, we have an interest in diagnosing opportunistic infections in other immunosuppressed groups.17–19 We used these same techniques to diagnose infection in our sarcoidosis patients.

Several immunosuppressive agents are effective for the treatment of sarcoidosis. These agents include corticosteroids,2 methotrexate,20 hydroxychloroquine,21 azathioprine,22 leflunomide,23 cyclophosphamide,24 thalidomide25 and infliximab.26 The widespread use of these drugs reflects the tertiary status of this clinic.27

The only cases of opportunistic infections occurred in patients treated with glucocorticoids, with or without methotrexate. This was the most commonly used treatment regimen at our institution, and hence may represent the highest exposure for patients. Interestingly, we did not see any invasive infections among the 29 patients treated with infliximab.

The treatment for these fungal infections included reducing the immunosuppression as well as antifungal therapy. For those patients receiving both methotrexate and prednisone, methotrexate was discontinued.

One patient experienced a relapse of *B. dermatitides* infection after stopping itraconazole. An additional patient with *C. neoformans* pneumonia had a past history of *C. neoformans* pneumonia two years prior to this episode while on corticosteroids. Three other patients have discontinued azoles after a year of treatment. These three patients did not show evidence of recurrent infection for at least a year after stopping antifungal therapy. Discontinuation...
of anti-fungal therapy for a patient who remains on immunosuppressant therapy may be associated with recurrence of the fungal infection.

Three of the seven immunosuppressive cases were due to *C. neoformans* infection. An increased risk for cryptococcal infection in sarcoidosis patients has been suggested by other investigators.28,29,13,30 One possible mechanism for this increased frequency may relate to the sarcoidosis itself.31 However, glucocorticoids can also increase the risk for cryptococcal infection. Only one of the seven patients was leucopenic at the time of diagnosis of opportunistic pneumonia. This patient had a white blood cell count between 2000–2500 cells/mm³ prior to starting on methotrexate 2.5 mg/week, and his white blood cell count remained unchanged while on methotrexate. Unfortunately, he developed *C. neoformans* pneumonia 6 months after starting methotrexate. However, he had previously developed *C. neoformans* while on prednisone alone.

The diagnosis of disseminated histoplasmosis represents a clinical dilemma.8 Histoplasmosis can cause a sarcoid-like granulomatous reaction.14 In our two cases, the referring physicians attributed the patients’ declining status to sarcoidosis and therefore increased the corticosteroid dosage. The fact that the patients were getting worse despite high-dose corticosteroids suggested an alternative diagnosis. Disseminated intravascular coagulopathy, a condition which we have not seen with sarcoidosis, developed in both of these cases.

Although aspergillomas were diagnosed in seven patients in this study, none of them developed invasive aspergillus during the observation time. All seven patients had fibrotic lung disease and received corticosteroids. Reports suggest that sarcoidosis patients with aspergillomas may develop invasive disease.32 However, this did not occur in our patients, perhaps reflecting our routine usage of itraconazole for aspergillosis.33

In conclusion, patients treated with immunosuppressive therapy including corticosteroids for sarcoidosis may develop invasive fungal infections. The relative risk compared to other conditions treated with high dose prednisone is hard to quantify, since the corticosteroid dosage schedule is different from conditions such as rheumatoid arthritis, where lower doses of prednisone are used. All of our patients were receiving corticosteroids at the time of opportunistic infection. Although some of the patients were also receiving methotrexate, fungal infections did not occur when patients were receiving other immunosuppressive agents, including infliximab. A high level of suspicion is necessary in identifying these patients, as the clinical presentation can mirror disease progression. The failure of sarcoidosis patients to respond to immunosuppressive therapy should raise the suspicion for an underlying opportunistic infection.

References
19. Sternberg RJ, Baughman RP, Dohn MN, First MR. Utility of bronchoalveolar lavage in assessing pneumonia in...


