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Management of asymptomatic coccidioidomycosis in patients with rheumatic diseases

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Abstract

Coccidioidomycosis is an endemic fungal infection common in the southwestern United States. Some rheumatology clinics periodically screen patients with coccidioidal serology, resulting in the identification of patients who are serologically positive but without clinical symptoms. The management of such patients is unclear. A retrospective study was conducted between 2007 and 2015 at two arthritis centers in Tucson, Arizona. The asymptomatic patients were identified who were receiving disease-modifying antirheumatic agents and had a positive coccidioidal serology. Serological testing including IgM and IgG was performed by enzyme immunoassay (EIA), immunodiffusion (IDTP and IDCF), or complement fixation. Out of 71 patients who were identified with positive coccidioidal serologies, 19 were asymptomatic. 18/19 patients continued antirheumatic therapy, 13 without interruption. 13/19 patients received no antifungal treatment, including 10 who remained on antirheumatic treatment. The other six were started on fluconazole, ranging from 8 to 73 months (median 30.5 months). After a median follow-up of 43 months, no patient developed clinically active coccidioidomycosis. Overall, 14 had only a positive EIA serological test. These results suggest that continued antirheumatic therapy is safe in asymptomatic patients with positive coccidioidal serological tests and that routine implementation of antifungal treatment may not always be warranted. The findings also raise concern regarding the utility of routine serological testing of asymptomatic patients residing in the coccidioidal endemic area, mainly using the EIA test.

Keywords Biologic drugs · Coccidioidomycosis · Antirheumatic agents · Rheumatic diseases/drug therapy · Coccidioidomycosis/therapy · Coccidioidomycosis/immunology

Introduction

Coccidioidomycosis, also known as Valley fever, is an infection caused by the soil-dwelling fungi *Coccidioides*. The infection occurs endemically in parts of central and southern California, the deserts of Arizona, southern New Mexico, southwestern Utah, western Texas, as well as in northern Mexico and portions of Central and South America [1]. It is estimated that there are at least 150,000 infections annually in the United States, with most occurring in the known endemic regions [2]. The incidence appears to be increasing [3]. Approximately, more than half of the infected individuals remain asymptomatic [4, 5]. For those who develop symptoms, the clinical presentation ranges from a syndrome of community-acquired pneumonia to disseminated extrathoracic disease [6]. Disseminated disease may occur in an otherwise healthy individual, but is increased among patients with suppressed cellular immunity [7].

In the last decade, biological disease-modifying antirheumatic drugs (bDMARDs) have shown promising outcomes in rheumatic diseases and are an integral part of most therapeutic strategies. These agents act by modifying, altering, or suppressing the immune system. These include tumor

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necrosis factor-α (TNF-α) antagonists (etanercept, infliximab, adalimumab, golimumab, and certolizumab), anti-B cell therapy (rituximab), soluble inhibitors of T cell activation (abatacept), antibodies directed against interleukin-6 (tocilizumab), and others. While the addition of bDMARDs to the therapeutic armamentarium of rheumatic diseases has revolutionized the existing treatment strategies, it has also increased the risk of developing symptomatic coccidioidomycosis among patients living in the coccidioidal endemic regions. The risk of symptomatic coccidioidomycosis in patients treated with TNF-α antagonists is thought to be 1–2% per year with an increased risk of developing the extrathoracic disseminated disease compared to the general population [8, 9]. As with other fungal infections, the risk may be increased further when bDMARDs are used in conjunction with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and hydroxychloroquine; even csDMARDs without biologics [10].

The current Infectious Diseases Society of America (IDSA) clinical practice guidelines for the treatment of coccidioidomycosis recommends screening with *Coccidioides* serology before initiation of bDMARDs [2] in the coccidioidal endemic areas. It is a common practice in these regions to repeat such testing annually, including at our institutions [2, 11, 12]. The subsequent management of patients who develop a positive test and are asymptomatic is challenging considering the lack of evidence-based guidelines [2, 12, 13].

The aims of this study were as follows: (1) to determine the optimal management strategies for asymptomatic patients with positive coccidioidomycosis serologies receiving treatment with csDMARDs and/or bDMARDs; and (2) to establish the role of serological testing for coccidioidomycosis in asymptomatic patients on csDMARDs and/or bDMARDs.

Materials and methods

The study was performed at two centers affiliated with the University of Arizona between the years 2007 and 2015. After obtaining Institutional Review Board approval [Protocol Number: 1200000321A006 (Revised: January 19, 2018)] at the University of Arizona, a chart review of patients in both inpatient and outpatient settings was conducted. The patients were searched by reviewing the electronic medical records (EMR) of all patients seen at least once between 2007 and 2015 who developed serologic and/or clinical evidence of coccidioidomycosis while being treated with bDMARDs including infliximab, adalimumab, etanercept, golimumab, abatacept, rituximab, tocilizumab, with or without csDMARDs, including methotrexate, leflunomide, and azathioprine.

The data were extracted using a structured template that included age, sex, race/ethnicity, bDMARDs and csDMARDs that were used to treat the particular patient, underlying diagnosis requiring the bDMARDs and csDMARDs treatment, mode of diagnosis (serologic testing) of coccidioidomycosis infection, imaging studies relative to the diagnosis of coccidioidomycosis, clinical manifestations of coccidioidomycosis (if any), antifungal therapy, and its duration (if used), management of bDMARDs and csDMARDs after the diagnosis of coccidioidomycosis, and follow-up serologic testing for coccidioidomycosis (if available). This information was used to identify the patients who were asymptomatic with positive serum antibodies to coccidioidomycosis. The clinical course and therapeutic strategies adapted for these patients were reviewed in the context of the suggested protocol for managing these patients in 2012 [12].

Coccidioidal serologic testing was performed at a variety of sites; four at LabCorp, and five at Sonora Quest Laboratories. Two patients were seen at SAVAHCS where a non-proprietary immunodiffusion assay was performed without enzyme immunoassay (EIA). The coccidioidal serologic testing site information was not available for eight patients.

Definitions

Coccidioidomycosis was diagnosed by at least one of the following: any positive coccidioidal serologic test (enzyme immunoassay (EIA), immunodiffusion (ID), or by complement fixation); a positive fungal culture; detection of spherules in a tissue or fluid specimen; or clinical diagnosis by a highly experienced clinician. Coccidioidomycosis is said to be asymptomatic if the only criterion met is a positive serologic test. Pulmonary coccidioidomycosis was defined as a positive test plus a new radiographic finding with or without lower respiratory symptoms, a rash compatible with erythema nodosum, fever, or night sweats. Disseminated coccidioidomycosis was defined as a positive culture or histologic finding from a nonpulmonary site [2, 12].

Ethical statement

The project was approved by the University of Arizona Human Subjects Protection Program, and all procedures performed in the study involving human participants were following the ethical standards of the University of Arizona. This article does not contain any studies with animals performed by any of the authors.

Results

Between 2007 and 2015, we found 71 patients with positive coccidioidal serology tests and, after medical record review, identified 19 patients who were without symptoms while receiving treatment with a bDMARD, a csDMARD, or a combination of these agents. The total number of patients who underwent testing by coccidioidal serology could not be determined. Six of these 19 cases were included from a previously published study [9] but now have longer follow-up.

Rheumatoid arthritis was the most common rheumatologic disorder, occurring in 17 patients. One patient had dermatomyositis, and one had psoriatic arthritis. Twelve of the 19 patients were Caucasian and over the age of 50 years (Table 1). Eight patients had positive IgM EIA alone, four patients had a positive IgG EIA alone, two patients were both IgM and IgG EIA positive, two patients were both IgM EIA and complement fixation positive, two patients were immunodiffusion positive alone, and one patient was positive for both immunodiffusion and complement fixation.

Specific details of management are displayed in Table 2. Eight patients were on monotherapy with a bDMARD, nine were on a combination of a bDMARD, and a csDMARD and two were on monotherapy with a csDMARD. Six patients stopped their antirheumatic therapy, three of whom were on infliximab (two on monotherapy and one on combination therapy with methotrexate), two were on adalimumab (one on monotherapy and one on combination therapy with methotrexate), and one on etanercept combination therapy with methotrexate and hydroxychloroquine. The remaining 13 patients continued antirheumatic therapy without any interruption. Among the six patients in whom antirheumatic treatment was interrupted, it was restarted in five, most resuming therapy within 1 month (range 0.5–12 months). One did not resume therapy due to osteonecrosis of jaw and concern for concomitant bacterial infection.

Six of the 19 patients received fluconazole, ranging from 8 to 73 months (median 30.5 months). Three of the six patients started on fluconazole had positive immunodiffusion serology. There were no other apparent clinical characteristics associated with initiating fluconazole therapy. Three of the six patients on fluconazole were on monotherapy with infliximab, two were on monotherapy with methotrexate, and one was on a combination of infliximab and methotrexate. In all instances, antirheumatic therapy was continued in patients on fluconazole. Overall, the median follow-up was 43 months. During this time, there was one death which was not related to coccidioidomycosis.

Table 1 Summary of characteristics of patients who were diagnosed with asymptomatic coccidioidomycosis during treatment with biologic response modifiers and/or disease-modifying antirheumatic drugs

Disease	*N*
Rheumatoid arthritis	17
Dermatomyositis	1
Psoriatic arthritis	1
Race/ethnicity	
Caucasian	12
Hispanic	5
African American	2
Age	
20–29	1
30–39	3
40–49	2
50–59	3
60–69	8
70–79	2

N number of patients

Discussion

The results of this study suggest that continued antirheumatic therapy is safe in asymptomatic patients with positive coccidioidal serological tests. Despite that fact there was no comparison to patients who received antifungals, our data suggest that routine implementation of antifungal treatment may not always be warranted. The findings also raise concern regarding the utility of routine serological testing of asymptomatic patients residing in the coccidioidal endemic area, mainly using the EIA test.

These findings support the management strategy proposed by Taroumian et al. that antirheumatic therapy might be continued in patients found to have positive coccidioidal serological tests but who were clinically asymptomatic [12]. Recently, Choi et al. conducted a retrospective study and concluded that patients who undergo screening for coccidioidomycosis before or during TNF-α antagonist treatment are less likely to develop symptomatic coccidioidomycosis than those who are not screened for this infection [13]. However, it was reported that 17 out of 925 screened patients were asymptomatic and had isolated EIA IgM. The TNF-α antagonist therapy was either immediately initiated or continued for all these patients. None of these 17 patients developed coccidioidal illness which is consistent with the results of our study.

Current guidelines are not clear about the initiation, continuation or discontinuation of antifungal therapy in patients on antirheumatic therapy who are found to have positive coccidioidal serologies without attributable signs or symptoms of coccidioidomycosis [2]. Interestingly, in the 11 patients in this study who did not receive antifungal therapy, the antirheumatic treatment was continued without an adverse outcome. None of these patients developed any clinical complication related to coccidioidal infection. As noted above, the study by Choi et al. identified

Table 2 Description of the 19 cases

No	Serological result	F/u serology (month f/u, type of test)	Anti-rheumatic therapy	At time of coccidioidal diagnosis	Subsequent management	Antifungal therapy	Antifungal duration (mos)	Follow-up (mos)
1	IDTP, IDCF and CF	2 months: IgG EIA +, IgM EIA –	Infliximab	Stopped	Restarted within 1 mos combined with MTX	Fluconazole	62	68
2	IgM EIA, CF	1 month: IgM EIA –, IgG EIA –	Adalimumab + MTX	Adalimumab stopped MTX continued	Adalimumab resumed within 1 mos with MTX	None	N/A	67
3	IgM EIA, CF	47 months: IgM EIA –, IgG EIA –	Infliximab	Continued	Continued	None	N/A	47
4	IgM EIA	3 months: IgM EIA +	Infliximab + MTX	Both continued	Both continued	Fluconazole	13	80
5	IgM EIA	1 month: IgM EIA +	Etanercept + MTX + HCQ	All continued	Etanercept and MTX stopped; HCQ restarted	None	N/A	47
6	IgM EIA, IgG EIA	4 months: IgM EIA +	Infliximab	Stopped	Restarted after 2 weeks	Fluconazole	9	55
7	IgM EIA	12 months: IgM EIA +	Infliximab + MTX	Both stopped	Infliximab restarted after 11 mos; MTX after 16 mos	Fluconazole	34	92
8	IgM EIA	2 months: IgM EIA +	Infliximab + MTX	Both continued	Both continued	None	N/A	43
9	IgM EIA	No repeat	Abatacept + MTX	Both continued	Both continued	None	N/A	30
10	IgM EIA, IgG EIA	10 months: IgM EIA –, IgG EIA -	Golimumab + MTX + HCQ	All continued	All continued	None	N/A	39
11	IgG EIA	7 months: IgG EIA –	Adalimumab	Stopped	Restarted after 10 mos	None	N/A	25
12	IgG EIA	20 months: IgM EIA –, IgG EIA -	Rituximab	Continued	Continued	None	N/A	35
13	IDCF, CF	72 months: IgM EIA –, IgG EIA –	MTX	Continued	Continued with addition of adalimumab	Fluconazole	19	86
14	IDCF, CF	15 months: + IDCF	MTX	Continued	Continued	Fluconazole	68	116
15	IgG EIA	12 months: IgM EIA –, IgG EIA indeterminate	Tocilizumab	Continued	Continued	None	N/A	43
16	IgM EIA	20 months: EIA IgM EIA –	Rituximab + MMF	Both continued	Both continued	None	N/A	35
17	IgM EIA	6 months: IgM EIA +	Tocilizumab + MTX	Both continued	Both continued	None	N/A	6
18	IgG EIA	1 month: IgG EIA –	Adalimumab	Continued	Continued	None	N/A	32
19	IgM EIA	No repeat	Adalimumab	Continued	Continued	None	N/A	6

BRMs Biological response modifiers, *mos* month, *MTX* methotrexate, *HCQ* hydroxychloroquine, *MMF* mycophenolate mofetil, *IDTP* immunodiffusion IgM, *IDCF* immunodiffusion IgG, *CF* complement fixation, *EIA* enzyme immunoassay

17 patients as asymptomatic with positive coccidioidal serologies. The results demonstrated that 13/17 (76%) were not treated with antifungal therapy and no complications were observed related to coccidioidal infection during study duration [13]. These findings support the results of our study and indicate that there may be a limited role of antifungal therapy in asymptomatic patients with positive coccidioidal serologies.

The majority of patients in this study were seropositive for either IgM or IgG by EIA alone. In this group, none were started on antifungal treatment, and all continued their antirheumatic therapy, and all did well. There has been concern that an isolate IgM EIA test may be a false-positive finding [14, 15], but this has not been shown for IgG by EIA. Our findings raise concern regarding the utility of using IgM and IgG by EIA alone to diagnose coccidioidomycosis in asymptomatic patients. It should be noted that Choi and colleagues did not consider patients as having a coccidioidal infection based on EIA serology alone [13].

The limitations of this study include its retrospective nature and the relatively small sample size. Due to this, we are mindful not to generalize the results to other groups patients without rheumatic disease. The risk of the disseminated disease appears to higher in African Americans and Filipinos compared to other groups [16], and these populations were under-represented in our study. Moreover, the decision regarding both antirheumatic and antifungal therapy was made by individual clinicians based on unmeasured clinical and patient factors that could have resulted in a bias. Finally, the total number of patients who were initially screened by coccidioidal serology could not be determined. Due to this, the prevalence of positive serological tests, as well as the proportion without attributable signs or symptoms of active coccidioidomycosis, could not be ascertained.

The introduction of biological therapies has transformed the ability to treat the rheumatic diseases effectively, but associated increased risk of infection poses a considerable challenge in daily clinical practice. Therefore, the coccidioidal infection will continue to be an essential part of the management strategies in patients living in endemic areas. Future studies are needed to determine the significance of positive serologies in immunosuppressed patients with rheumatic disease, and the safest management strategy. Moreover, the utility of serologic testing, particularly using EIA, as a screening tool merits reconsideration. The findings of this study can potentially guide researchers in this area, and the upcoming clinical studies will have more clear and definitive answers.

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Compliance with ethical standards

Conflict of interest Bilal J, Kollampare S, Bode B, Lisse J, Hoover SE, and Sudano D. Ampel NM declare that they have no conflict of interest related to this study.

Related abstract publications/poster presentations Management of Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease. 2014 ACR/ARHP Annual Meeting. The related abstract publication is following: Sudano, Dominick, et al. "management of Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease.: 2205." Arthritis & Rheumatology 66 (2014): S961.Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease: 8 Years of Experience. 2016 ACR/ARHP Annual Meeting [Abstract Number: 1350]. The related abstract publication is following: Ajaz U, Lisse JR, Ampel NM, Sudano D. Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease: 8 Years of Experience [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). The Value of Routine Serological Screening for Coccidioidomycosis in Patients On Antirheumatic Therapy. 62nd Annual Cocci Study Group Meeting in Flagstaff, Arizona on April 13–14, 2018.

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