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BRIEF REPORT

Coccidioidomycosis in Patients Treated With Ruxolitinib

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We report 8 cases of coccidioidomycosis associated with ruxolitinib treatment. Among 135 patients living in the coccidioidal-endemic region receiving ruxolitinib, 5 cases were diagnosed after starting and 4 had extrathoracic dissemination. Periodic serological screening while on ruxolitinib is warranted for patients residing in the coccidioidal-endemic region.

Keywords. coccidioidomycosis; fungal infections; immunocompromised host; ruxolitinib.

Ruxolitinib, a Janus-activated kinase (JAK) 1 and 2 inhibitor, was introduced in 2011 for the treatment of myelofibrosis and high-risk polycythemia vera (PV). Its use has recently expanded to corticosteroid-refractory graft-vs-host disease (GVHD) and essential thrombocythemia. Given its mechanism of action on the immune system, increased rates of viral, bacterial, and fungal infections might be expected and have been described. The most frequently encountered infections include tuberculosis, cryptococcosis, and hepatitis B reactivation [1]. Although the risk of infections associated with ruxolitinib is clearly increased, it has not been accurately quantified [2].

Coccidioidomycosis is a fungal infection endemic to the Southwestern United States, particularly the San Joaquin Valley of California and the southcentral area of Arizona [3]. Primary infection occurs in the lungs, but dissemination beyond the thoracic cavity may occur and is increased in patients with compromised cellular immune function [4]. To date, no cases of coccidioidomycosis have been directly associated with ruxolitinib use. After we identified 3 cases of disseminated coccidioidal infection at our institution, we sought to determine if the overall rates of symptomatic coccidioidomycosis were increased among those on ruxolitinib and if their manifestations of illness were more severe than expected. Here, we describe our experience over a 12-year period among patients living in the coccidioidal-endemic region.

METHODS

We conducted a retrospective electronic health record search to identify patients seen at the Mayo Clinic in Arizona from 2007 to 2019 who received ruxolitinib. All charts were reviewed for demographic and clinical data. Variables catalogued included date and dosage of ruxolitinib therapy, reason for therapy, and use of other immunosuppressive agents. We additionally collected coccidioidal serology results before ruxolitinib therapy as well as any subsequent serologies during ruxolitinib treatment. Patients were included for analysis if their primary residence was in the Southwestern United States (Arizona, California, Nevada, New Mexico, Texas, and Utah), if they received comprehensive care at our institution, and if they received >30 days of ruxolitinib therapy.

RESULTS

We identified 190 patients who had received ruxolitinib therapy from January 1, 2007, through May 25, 2019. Among these, 55 were excluded because of residence outside of the Southwestern United States, lack of follow-up, or therapy for ≤30 days. Of the remaining 135 patients, the indications for ruxolitinib included myelofibrosis, PV, GVHD, and essential thrombocythemia. Ruxolitinib dosage ranged from 5 mg twice daily to 20 mg twice daily, with a median dose of 10 mg twice daily.

We identified a total of 8 cases of coccidioidomycosis. The cases are summarized in Table 1. None has been previously published. Among these patients, 4 had a diagnosis of coccidioidomycosis preceding the use of ruxolitinib. The diagnosis was initially based on a compatible clinical syndrome and positive coccidioidal serologies. Three were continued on antifungal therapy and remained asymptomatic. One patient (Case 4) was prescribed antifungal therapy for 1 year. Ruxolitinib was started 5 years later. Coccidioidal serologies were negative at that time. Two years later, the patient presented with a large retropharyngeal abscess and erosions of the right scapula and the second and third cervical vertebrae. The abscess drainage was culture-positive for *Coccidioides*.

Among the other 4 cases, the time after starting ruxolitinib to the identification of clinically active coccidioidomycosis ranged from 1 month to 1 year. None was receiving antifungal

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Table 1. Summary of Cases of Coccidioidomycosis on Ruxolitinib

Case	Age, y	Sex	Race	Indication	Ruxolitinib Dose	Other Immunosuppressives	Time to Coccidioidomycosis	Antifungal Prophylaxis	Type of Coccidioidomycosis	CF at the Time of Diagnosis	Subsequent Antifungals	Change in Ruxolitinib Dose
1	63	F	White	Myelofibrosis	15 mg BID	None	Preceded	Fluconazole	Primary pulmonary	NA	Fluconazole	10 mg BID
2	49	M	White	GVHD	5 mg BID	Tacrolimus	Preceded	Fluconazole	Primary pulmonary	NA	Fluconazole	10 mg daily
3	63	M	White	GVHD	5 mg BID	Sirolimus	Preceded	Posaconazole	Primary pulmonary	NA	Posaconazole	No change
4	72	M	White	Myelofibrosis	15 mg BID	None	Preceded; recurred 2 y after starting ruxolitinib	None	Multisite dissemination: retropharyngeal abscess and bony erosions of scapula and vertebrae (culture positive from retrophyangeal abscess)	1:512	Amphotericin B (kidney dysfunction) Itraconazole (fluid overload) Voriconazole (phototoxicity) Posaconazole	Discontinued
5	66	M	White	GVHD	5 mg BID	Tacrolimus, MTX	1 mo	None	Bilateral pulmonary nodules (culture positive from BAL)	<1:2	Isavuconazole (drug interaction) Fluconazole	Discontinued
6	64	M	White	Myelofibrosis	20 mg BID	None	1 y	None	Multisite dissemination: vertebrae, skin (vertebrae biopsy with cocci spherule, culture positive from skin)	1:256	Fluconazole Itraconazole	Unknown
7	66	M	White	Myelofibrosis	15 mg BID	None	6 mo	None	Multisite dissemination: liver and spleen (culture positive from hepatic lesion)	1:128	Amphotericin B with Itraconazole (cost-prohibitive) Fluconazole	Discontinued
8	84	M	Asian	Myelofibrosis	20 mg BID	None	1 y	None	Skin (culture positive)	1:64	Fluconazole	Discontinued

Abbreviations: BID, twice daily; CF, coccidioidal complement-fixing titer; F, female; GVHD, graft-vs-host disease; M, male; MTX, methotrexate; NA, not applicable.

prophylaxis while on ruxolitinib. Only 1 was receiving another immunosuppressive agent (Case 5). All 4 presented with extrathoracic dissemination, and 3 had multiple anatomic sites involved. Sites of dissemination included the skin, bones, liver, and spleen.

In all cases of disseminated disease, biopsies of extrathoracic sites were culture-positive for *Coccidioides,* and bronchoalveolar lavage fluid grew *Coccidioides* in the patient with multiple pulmonary nodules. Coccidioidal complement fixation antibodies were detected in all 4 patients with extrathoracic dissemination and ranged from 1:64 to 1:512. All patients received antifungal therapy after the diagnosis of coccidioidomycosis, and all were alive at the time of analysis. In 4 instances, ruxolitinib was discontinued; the dose was reduced in 2 and remained unchanged in 1. In 1 case, dosing changes could not be ascertained.

DISCUSSION

We identified a total of 8 cases of coccidioidomycosis among patients receiving ruxolitinib therapy and living in the coccidioidal-endemic region. Among these, 5 were identified after ruxolitinib was started and 4 developed disseminated disease. The 5 active cases of coccidioidomycosis represent nearly 3% of the patients receiving ruxolitinib in this cohort. This is well above the estimates for symptomatic coccidioidomycosis in the general population, which range from 0.1% to 0.4% [3] and are similar to rates observed among transplantation recipients [5]. Based on this, we believe that ruxolitinib represents a significant risk for the development of symptomatic and disseminated coccidioidomycosis among patients living in the coccidioidal-endemic region. The risk seems particularly related to ruxolitinib because only 1 of the 5 cases who developed symptomatic coccidioidomycosis after starting ruxolitinib was receiving any other immunosuppressive medication.

Three of 4 patients with a history of pulmonary coccidioidomycosis who received preventive antifungal therapy did not develop symptomatic coccidioidomycosis after starting ruxolitinib, while the patient not on antifungal prophylaxis developed extrathoracic dissemination 2 years after ruxolitinib initiation. These results suggest that antifungal prophylaxis might be beneficial in controlling reactivation in patients receiving ruxolitinib with prior active coccidioidal infection. Such an approach has recently been shown to be effective among liver transplant recipients [6]. However, care should be exercised when combining these 2 agents because of possible drug interactions [7].

Although this is the first report of coccidioidomycosis occurring among patients receiving ruxolitinib, this medication has been used in 1 patient with multisite disseminated coccidioidomycosis associated with a *STAT1* gain-of-function mutation. In that case, even though STAT1 phosphorylation levels normalized after ruxolitinib was started, the patient developed a new site of coccidioidal infection and the drug was subsequently discontinued [8]. It is not surprising that use of ruxolitinib would be associated with the development of severe and disseminated coccidioidomycosis. Through its mechanism of inhibiting JAK 1 and 2, it impairs the interleukin-12/interferon-γ pathway, which appears to be critical for the development of protective coccidioidal immunity [9].

Our data indicate that close monitoring for coccidioidomycosis, including serological testing before initiation of therapy and possible periodic subsequent testing during therapy, should be done for all patients on ruxolitinib who have possible exposure to *Coccidioides*. That all patients with extrathoracic dissemination manifested positive coccidioidal serologies suggests that periodic monitoring of serology could be an appropriate means of detected impending active coccidioidomycosis in patients receiving ruxolitinib. This is currently not recommended by the most recent IDSA clinical guidelines on coccidioidomycosis for the management of patients on biological response modifiers [10]. In addition, antifungal therapy should be initiated in all of those with evidence of coccidioidomycosis, including those with isolated positive coccidioidal serologies, while on ruxolitinib. Whether all patients living in the coccidioidal-endemic region who receive ruxolitinib should receive antifungal prophylaxis in the absence of documented active coccidioidomycosis cannot be answered at this time, but it may be prudent. Finally, all patients prescribed ruxolitinib residing in the coccidioidal-endemic region should be counseled about the possible risk of severe and disseminated disease.

Our study is limited by its retrospective nature and relatively small sample size. Although we manually examined each chart included for analysis, we cannot be completely certain of patient adherence to medication unless it was otherwise mentioned in the chart. Further studies should follow patients receiving ruxolitinib prospectively and obtain pretreatment and subsequent coccidioidal serology on all such patients.

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