Histoplasmosis Following Systemic Immunomodulatory Therapy for Ocular Inflammation

MATTHEW R. STARR AND WENDY M. SMITH

• PURPOSE: Histoplasmosis is a known complication of systemic immunosuppressive therapy, particularly among patients who are receiving tumor necrosis factor α inhibitors. There are limited data on the development of disseminated or pulmonary histoplasmosis among patients who are receiving systemic immunosuppressive medication for noninfectious ocular inflammation.
• DESIGN: Retrospective case series.
• METHODS: We reviewed all patients with uveitis or scleritis who subsequently developed pulmonary or disseminated histoplasmosis at the Mayo Clinic in Rochester, Minnesota between September 1, 1994 and July 1, 2017, with a 3:1 age- and sex-matched control cohort who did not develop histoplasmosis. This was a single institutional study examining patients that developed histoplasmosis after the initiation of systemic immunomodulatory therapy (IMT). Patients had to develop either disseminated or pulmonary histoplasmosis while receiving systemic immunosuppressive therapy and have an ophthalmic examination at Mayo Clinic Rochester. The control group was comprised of patients who received systemic IMT for ocular inflammation but did not develop histoplasmosis.
• RESULTS: Nine cases of histoplasmosis were identified: 2 disseminated and 7 pulmonary. Both patients with disseminated histoplasmosis were taking tumor necrosis factor α inhibitors. Seven of the 9 patients received systemic antifungal medication, including both disseminated cases. Over a median follow-up of 4.4 years, none of the patients died, and there were no recurrences of histoplasmosis. When compared to the control cohort, there was no correlation between length of time on IMT and the risk of histoplasmosis.
• CONCLUSIONS: Ocular inflammation patients on systemic immunomodulatory therapy may develop pulmonary or disseminated histoplasmosis. Most cases require treatment with systemic antifungal medication, but it might not be necessary to stop systemic immunomodulatory medication for ocular inflammation. Ophthalmologists should be aware that patients receiving systemic immunomodulatory therapy have a higher risk of developing *Histoplasma* infections. Prompt diagnosis and treatment using the expertise of an infectious diseases specialist may ensure low mortality for these patients. (Am J Ophthalmol 2019;198:88–96. © 2018 Elsevier Inc. All rights reserved.)

HISTOPLASMA CAPSULATUM IS A FUNGUS MAINLY found in soil contaminated by bird or bat droppings in the Midwest United States along the Ohio and Mississippi River Valleys.[1] Histoplasmosis is most commonly acquired by inhalation of fungal spores. The pulmonary infection is typically asymptomatic or characterized by self-limited fever, cough, and fatigue; disseminated disease may present with shock, pancytopenia, and renal and hepatic failure.[2] It is well known that immunocompromised patients can develop symptomatic histoplasmosis,[3,4] but recent reports have also shown that patients who are taking systemic immunomodulatory medication (IMT) are also at risk for pulmonary and disseminated histoplasmosis.[5–7]

Most cases in the published literature involve patients treated with systemic IMT for diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and ankylosing spondylitis.[5–7] While systemic IMT is increasingly used to treat noninfectious ocular inflammation, there are few published reports of histoplasmosis complicating the systemic treatment of uveitis.[7,8] This study focuses solely on patients with primary ocular inflammation and describes the clinical characteristics and outcomes of those who developed pulmonary or disseminated histoplasmosis while receiving systemic IMT.

METHODS

THIS STUDY IS IN COMPLIANCE WITH THE HEALTH INSURance Portability and Accountability Act, received a prospective waiver from the Mayo Clinic Institutional Review Board, and adhered to the tenets of the Declaration of Helsinki. We performed a retrospective case series of all patients who were diagnosed with uveitis and systemic

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From the Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, USA.

Inquiries to Wendy M. Smith, Mayo Clinic, Department of Ophthalmology, 200 First St SW, Rochester, MN 55905, USA; e-mail: smith.wendy1@mayo.edu

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TABLE 1. Demographic Data for All Patients Who Developed Systemic Histoplasmosis While Treated With Systemic Immunomodulatory Therapy for Ocular Inflammation

Male, n (%)	6 (66.7)
Age at diagnosis of histoplasmosis, y (mean ± SD)	41.8 ± 15.0
Time from initiation of systemic IMT to diagnosis of histoplasmosis infection, y (range)	1.9 (1.2-6.1)
Length of follow-up after infection, y (range)	4.4 (0.7-8.4)
Attack rate, events per year (Poisson 95% confidence interval)	0.0893 (0.04-0.17)

IMT = immunomodulatory therapy; SD = standard deviation.

histoplasmosis at the Mayo Clinic using the advanced cohort explorer (ACE). ACE is a data repository from multiple sources within Mayo Clinic Rochester that was initiated in 1994. We searched the database from September 1, 1994 through July 1, 2017. Using the ACE software we identified all patients with a diagnosis of systemic histoplasmosis and intraocular inflammation, including anterior uveitis, iritis, intermediate uveitis, posterior uveitis, panuveitis, retinitis, and retinal vasculitis. The charts were reviewed to confirm the diagnoses. Diagnosis was made typically via serologies, chest radiograph, computed tomography findings, bronchoalveolar lavage (BAL), or lung biopsy. The following inclusion criteria were required: (1) the patient had to have an ophthalmologic examination at Mayo Clinic Rochester, (2) the ocular inflammation was treated with systemic IMT, and (3) pulmonary or disseminated histoplasmosis was diagnosed after systemic IMT was initiated. A 3:1 age- (within 5 years) and sex-matched control cohort was created using a similar search within the ACE database, except we did not include histoplasmosis within the search criteria. These patients were also required to have had an ophthalmologic examination at Mayo Clinic and were treated with systemic IMT for ocular inflammation. The data were collected and entered into Microsoft Excel 2010 (Microsoft Corporation; Redmond, WA, USA). We used a Poisson confidence interval to estimate the attack rate of a systemic histoplasmosis infection while on systemic IMT. Comparisons between the case cohort and control cohort were performed using the Fisher exact test, and $P < .05$ was considered statistically significant.

RESULTS

THE INITIAL SEARCH IDENTIFIED 17,758 PATIENTS WITH intraocular inflammation; 137 also had a diagnosis of histoplasmosis, but only 9 patients met the study inclusion criteria. The average age of the patients was 41.8 ± 15.0 years, and 6 were male (66.7%). The median time from initiation of systemic IMT to the diagnosis of histoplasmosis was 1.9 years (1.2 and 6.1 years [25th and 75th quartiles, respectively], range 0.6-16.5 years). The median follow-up time was 4.4 years (0.7 and 8.4 years [25th and 75th quartiles, respectively]); there were no deaths. The attack rate was 0.0893 events per year with a Poisson 95% confidence interval of 0.04 to 0.17 (Table 1).

There were 7 cases of pulmonary histoplasmosis and 2 cases of disseminated histoplasmosis (Table 2). All 9 of the patients lived in *Histoplasma*-endemic areas of the upper Midwest United States. All of the patients had abnormal chest imaging studies; 6 patients had lung biopsies or bronchoalveolar lavage specimens that were positive for *Histoplasma*. Of the 7 patients who presented with symptoms (2 disseminated and 5 pulmonary), all had fevers. The 2 asymptomatic patients had pulmonary histoplasmosis, and antifungal therapy was not initiated. All other cases of pulmonary histoplasmosis were treated with oral itraconazole. Five of the 9 patients were receiving TNFα inhibitors: 3 on infliximab and 2 on adalimumab. Three of the patients taking TNFα inhibitors had pulmonary histoplasmosis; the TNFα inhibitors were discontinued in all 3 cases. Both of the disseminated histoplasmosis cases occurred in patients who were taking TNFα inhibitors, and both were initially treated with intravenous amphotericin. The clinical details of the 2 patients with disseminated histoplasmosis are discussed in more detail below.

• **DISSEMINATED HISTOPLASMOSIS (CASE 1):** Patient 4 was a 49-year-old man with chronic bilateral diffuse anterior scleritis complicated by uveitis and macular edema. Evaluations for infectious etiologies and systemic inflammatory disease were negative. High-dose oral prednisone was required to control the scleritis. Because of the inability to taper to low-dose systemic corticosteroids within 3 months, subcutaneous methotrexate was initiated. After >3 months on methotrexate, the scleritis and macular edema continued to recur when oral prednisone was decreased; therefore, adalimumab 40 mg every other week was added. After 3 months of adalimumab and methotrexate therapy, the scleritis was quiescent, and prednisone was <20 mg daily.

The patient presented to the emergency department with a fever, a history of unintentional weight loss, dyspnea, and abdominal pain. Laboratory values were significant for normocytic anemia (hemoglobin 11.7 g/dL [normal 13.5-17.5 g/dL]) and thrombocytopenia (77×10^9/L [normal 150-450 $\times 10^9$/L]) with a normal white blood cell count (4.5×10^9/L). He also had a transaminitis (alkaline phosphatase 206 U/L [normal 45-115 U/L], alanine transaminase 179 U/L [normal 7-55 U/L], and aspartate transaminase 142 U/L [normal 8-48 U/L]). A computed tomography scan of the chest revealed diffuse,

TABLE 2. Characteristics of Patients With Primary Ocular Inflammation Managed With Systemic Immunomodulatory Therapy That Developed Systemic Histoplasmosis Infections

Patient No.	Sex	Age at Histoplasmosis Diagnosis (y)	Ocular Diagnosis	Associated Systemic Disease	Time from Immunotherapy Initiation to Histoplasmosis Diagnosis (y)	Type of Histoplasmosis	Diagnosis of Histoplasmosis
1	M	24	Pars planitis	None	2	Pulmonary	Chest radiograph, positive serum histoplasma antibody
2	M	38	Anterior uveitis with retinal vasculitis, idiopathic	None	8	Pulmonary	Lung biopsy
3	F	50	Anterior scleritis and uveitis	Granulomatosis with polyangiitis	0.75	Pulmonary	Lung biopsy
4	M	50	Anterior scleritis and uveitis, idiopathic	None	0.9	Disseminated	Positive PCR from bronchoalveolar lavage and bone marrow, positive urine histoplasma antigen
5	M	36	Posterior uveitis with retinal vasculitis	Behçet disease	16	Disseminated	Bronchoalveolar lavage: positive PCR and culture; positive blood cultures, positive urine histoplasma antigen
6	M	51	Anterior uveitis	Crohn disease	10	Pulmonary	Chest radiograph, positive serum histoplasma antibody
7	M	19	Panuveitis, idiopathic	None	6	Pulmonary	Positive PCR from bronchoalveolar lavage, positive histoplasma urine antigen
8	F	56	Uveal effusion syndrome	Rheumatoid arthritis	0.6	Pulmonary	Positive PCR from bronchoalveolar lavage, positive serum histoplasma antibody
9	F	49	Panuveitis, idiopathic	None	4	Pulmonary	Chest computed tomography, positive serum histoplasma antibody, positive urine histoplasma antigen

F = female; M = male; PCR = polymerase chain reaction.

perihilar-predominant ground glass opacities with apical and basilar interlobular septal thickening, innumerable indeterminate tiny solid bilateral pulmonary nodules, and mediastinal lymphadenopathy. BAL yielded positive polymerase chain reactions (PCRs) and fungal cultures for *H capsulatum*. A bone marrow biopsy specimen was obtained, and it showed evidence of *Histoplasma*, confirming the diagnosis of disseminated histoplasmosis. Methotrexate and

(Continued)

Immunotherapy Agent at Time of Histoplasmosis Infection	Treatment of Histoplasmosis	Immunotherapy Stopped	Histoplasmosis Symptoms	Ocular Outcomes
Cyclosporine, oral prednisone	None	No	Asymptomatic	No light perception in either eye because of chronic total retinal detachments
Dapsone, oral prednisone	None	No	Asymptomatic	Developed uveitic glaucoma; retinal vasculitis quiescent
Methotrexate, oral prednisone	Itraconazole	Unable to taper oral prednisone	Cough and fever	Uveitis and scleritis quiescent
Methotrexate, adalimumab, oral prednisone	Amphotericin, itraconazole, and posaconazole	Stopped methotrexate and adalimumab, started mycophenolate mofetil, restarted adalimumab	Fever, lethargy, thrombocytopenia, and transaminitis	Scleritis and uveitis continue to recur, unable to taper to low dose prednisone
Infliximab	Amphotericin, itraconazole	Decreased infliximab dose and delayed infusion by 1 week	Fever, lethargy, and transaminitis	Mild, nonvisually significant increase in retinal vascular leakage on fluorescein angiography that resolved without change in treatment
Methotrexate, oral prednisone	Itraconazole	No	Cough and fever	Uveitis quiescent
Methotrexate, infliximab	Itraconazole and sulfamethoxazole/trimethoprim × 1 year	Stopped infliximab, continued methotrexate	Cough, fevers, chills	No increase in uveitis activity after discontinuation of infliximab, slowly decreasing methotrexate with plan to eventually discontinue
Methotrexate, adalimumab, oral prednisone	Itraconazole, posaconazole, fluconazole	Stopped methotrexate and adalimumab	Cough, fevers, chills: transaminitis attributed to medication not disseminated histoplasmosis	Initial diagnosis of uveitis incorrect; bilateral scleral windows for chronic uveal effusion with subsequent decrease in subretinal fluid, but significant vision loss because of prolonged presence of serous retinal detachments
Methotrexate, infliximab, oral prednisone	Itraconazole	Stopped methotrexate and infliximab	Cough, fevers, chills	Within 2 months of stopping methotrexate and infliximab, developed recurrent anterior uveitis; treated with increase in topical difluprednate eye drops and periocular triamcinolone injection (right eye only); 1 year after histoplasmosis diagnosis, started intravenous immunoglobulin infusions for common variable immune deficiency; eventually tapered off low-dose oral prednisone

adalimumab were discontinued, but oral prednisone was continued while intravenous amphotericin was started. He was subsequently transitioned to oral itraconazole, and then switched to oral posaconazole because of recurrent transaminitis. After a short period of quiescence, active scleritis recurred on oral prednisone monotherapy. Four months after the diagnosis of disseminated histoplasmosis, mycophenolate mofetil was added after a repeat

computed tomography scan of the chest and urine *Histoplasma* antigen studies confirmed that the infection was controlled on posaconazole. Despite mycophenolate mofetil 3000 mg daily, he continued to have recurrent scleritis and macular edema requiring high-dose oral prednisone. With the agreement of the infectious diseases department, adalimumab 40 mg every other week was restarted after 11 months on systemic antifungal medication.

• **DISSEMINATED HISTOPLASMOSIS (CASE 2):** Patient 5 was a 36-year-old man with Behçet disease diagnosed 16 years earlier when he presented with aseptic meningitis, posterior uveitis, retinal vasculitis, and oral ulcers. His inflammation was initially managed with chlorambucil and oral prednisone. After 2 years, he was transitioned from chlorambucil to methotrexate. Because of poor adherence to methotrexate and the development of recurrent uveitis, he was switched to intravenous infliximab 500 mg every 6 weeks with subsequent control of inflammation.

After taking infliximab for 10 years he presented with a 2-week history of fevers, chills, diarrhea, and a nonproductive cough. The laboratory workup revealed mild reactive lymphocytosis (12.4×10^9/L [normal $3.5\text{-}10.5 \times 10^9$/L]) and transaminitis (alkaline phosphatase 267 U/L [normal 45-115 U/L], alanine transaminase 200 U/L [normal 7-55 U/L], and aspartate transaminase 96 U/L [normal 8-48 U/L]). Chest radiographs demonstrated relatively diffuse solid nodules with mediastinal and hilar lymphadenopathy. Lung biopsy with BAL revealed non-necrotizing granulomas and granulomatous inflammation; silver staining showed fungal elements consistent with *H capsulatum*. The BAL PCR and cultures from BAL and blood were positive for *H capsulatum*, confirming the diagnosis of disseminated histoplasmosis.

Treatment was initiated with intravenous amphotericin followed by oral itraconazole. Because of the severity of previous inflammation that had resulted in significant central vision loss from macular scarring, infliximab infusions were resumed at a lower dose (400 mg, approximately 5 mg/kg, every 6 weeks) after a 1-week delay. Fluorescein angiography obtained 6 weeks later showed more peripapillary capillary leakage in the right eye, but there was no subjective or objective decrease in vision. Eleven months after diagnosis of disseminated histoplasmosis, there was no further increase in ocular inflammation or loss of vision. After 1 year of antifungal treatment, the dose of oral itraconazole was decreased by 50% and is anticipated to be continued indefinitely as long as the patient is receiving infliximab.

• **CONTROL SUBJECTS:** We were unable to completely match a 3:1 age- and sex-matched control cohort, but we were able to identify 24 control patients requiring systemic IMT for the management of their ocular inflammation who did not develop systemic histoplasmosis. The characteristics of their disease processes are presented in Table 3. The mean age (± standard deviation) of these patients at the time of their ocular disease diagnosis was 29.4 ± 14.2 years. Eight patients were female (33%) and these patients had a follow-up time of 8.3 ± 6.3 years. There was no significant difference in mean age ($P = .13$) or sex ($P = .85$). There were 16 control patients (66.7%) who had systemic disease necessitating the use of IMT. Of the 24 patients, 15 (62.5%) were managed with anti-TNF inhibitors. When comparing the person-time years of IMT, the 9 cases had a mean of 5.0 ± 5.1 years before the development of histoplasmosis, while the control cohort had a mean person-time years of IMT of 6.9 ± 5.2 years without the development of systemic histoplasmosis. There was no significant difference in the length of time on IMT among those patients who did not develop histoplasmosis versus those who did ($P = .33$).

DISCUSSION

HISTOPLASMOSIS IS AN ENDEMIC INFECTION IN THE Midwestern United States along the Ohio and Mississippi River valleys. An immunocompromised state, whether acquired through human immunodeficiency virus infection or iatrogenically induced via systemic IMT, is a risk factor for this infection. Over the past 30 years, systemic IMT has been increasingly used to treat noninfectious ocular inflammation. The number of ocular inflammation patients receiving systemic IMT is likely to rise because the TNFα inhibitor adalimumab recently became the first noncorticosteroid medication to be approved by the US Food and Drug Administration to treat noninfectious uveitis. Although a number of previous studies assessed histoplasmosis infections among patients with systemic inflammatory diseases, this is the largest single-center cohort study assessing patients with ocular inflammation who developed histoplasmosis while taking systemic IMT. In our study, the attack rate or development of histoplasmosis is rare, with an event rate of 0.0893 per year. We also did not find that patients who developed systemic histoplasmosis were on IMT for a significantly longer time than the control cohort. It would be plausible that being maintained on IMT for an extended period of time would increase the risk of developing histoplasmosis, but we did not find that the case cohort was maintained on IMT longer than the control cohort.

Granulomas are the primary immune response to eliminate fungal infections such as *Histoplasma*. Macrophages must recognize and engulf the fungus and then present antigens to T lymphocytes, which in turn promote granuloma formation and cytokine production to destroy the fungus.[9] TNF is pivotal during the early phases of granuloma formation because it is responsible for macrophage recruitment to the site of the infection and chemokine induction.[10] All

TABLE 3. Characteristics of Patients With Primary Ocular Inflammation Managed With Systemic Immunomodulatory Therapy Who Did Not Develop Systemic Histoplasmosis Infections

Patient No.	Sex	Age (y)	Ocular Disease	Associated Systemic Disease	Duration of Follow-Up (y)	Total Person-Years of IMT	Immunotherapy Agent
1	M	8	Posttransplant lymphoproliferative iritis	None	1.57	1.57	Rituximab, sirolimus
2	M	7	Chronic anterior uveitis	None	2.28	2.03	Methotrexate, prednisone, infliximab
3	M	9	Birdshot chorioretinopathy	None	10.74	10.29	Methotrexate, prednisone, infliximab
4	M	35	Vogt koyanagi harada	Multiple sclerosis	3.80	3.72	Prednisone, azathioprine
5	M	6	Idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis	Blau syndrome	11.26	6.43	Prednisone, methotrexate, adalimumab
6	M	10	Bilateral posterior scleritis	None	5.95	5.56	Methotrexate, prednisone, infliximab
7	F	39	Chronic anterior uveitis	Juvenile-associated rheumatoid arthritis	14.67	14.67	Methotrexate, prednisone, infliximab, adalimumab
8	F	49	Posterior uveitis	Lymphoproliferative enteropathy	6.05	5.89	Methotrexate, prednisone
9	M	21	Chronic anterior uveitis	None	5.51	3.90	Methotrexate, prednisone, infliximab
10	M	22	Sympathetic ophthalmia	None	0.29	0.27	Prednisone
11	F	32	Chronic HLA-B27 uveitis	Ankylosing spondylitis	22.55	10.73	Prednisone, methotrexate
12	F	50	Chronic anterior uveitis	Behçet disease	9.59	9.59	Methotrexate, prednisone, infliximab
13	M	26	Chronic anterior uveitis	Crohn disease	21.88	21.08	Prednisone, infliximab, azathioprine
14	M	31	Intermediate uveitis	Multiple sclerosis	17.88	10.85	Prednisone, methotrexate
15	M	34	Retinal vasculitis	Behçet disease	13.50	13.50	Prednisone, azathioprine, mycophenolate mofetil, cyclosporine
16	M	18	Retinal vasculitis	Rheumatoid arthritis	5.66	3.82	Prednisone, methotrexate, adalimumab
17	M	27	Chronic HLA-B27 uveitis	Crohn disease	13.22	12.26	Budesonide, adalimumab, certolizumab
18	M	31	Chronic anterior uveitis	Ulcerative colitis and ankylosing spondylitis	2.21	2.21	Prednisone, adalimumab, certolizumab, infliximab, methotrexate, etanercept
19	M	37	Chronic episcleritis	Relapsing polychondritis	1.84	1.84	Prednisone, methotrexate, mycophenolate mofetil, infliximab, cyclophosphamide
20	M	35	Chronic anterior uveitis	None	3.51	1.05	Prednisone, methotrexate, adalimumab
21	F	46	Chronic HLA-B27 uveitis	Ankylosing spondylitis	10.53	10.33	Prednisone, azathioprine, methotrexate, mycophenolate mofetil
22	F	37	Necrotizing scleritis	None	6.21	5.75	Prednisone, infliximab, methotrexate
23	F	51	Chronic anterior uveitis	Rheumatoid arthritis	3.94	3.94	Prednisone, methotrexate, infliximab, etanercept, adalimumab
24	F	44	Episcleritis	Relapsing polychondritis	5.27	5.27	Prednisone, mycophenolate mofetil

HLA-B27 = human leukocyte antigen-B27; IMT = immunomodulatory therapy.

the patients described in this series were taking systemic IMTs that can alter granuloma development. Prednisone and other glucocorticoids have a broad effect on the immune system, but most likely predispose patients to fungal infections because of a reduction in macrophage function and phagocytosis and a decrease in inflammatory cytokines, such as TNF.[11,12] Glucocorticoids also decrease interleukin-2 (IL-2),[13] which in turn decreases circulating T lymphocytes.[10] The relationship between IL-2 and T cells is more complex because IL-2 interacts with other regulatory T cells, and IL-2 blockade has been shown to incite an autoimmune inflammation.[14] Methotrexate is a well-known inhibitor of dihydrofolate reductase and has also been shown to decrease TNF.[15] Most TNFα inhibitors directly decrease circulating TNF as well. Overall, these systemic IMTs suppress granuloma formation and increase the risk of developing pulmonary and disseminated histoplasmosis.

Roach and associates showed that weaker infections can still be managed by granulomas lacking TNF induction, but more virulent diseases cannot be controlled adequately.[16] They postulated that the absence of TNF leads to a dysregulated immune response and granulomas lacking tight adhesion that are ineffective in containing bacterial infection. Previous studies have shown that patients taking TNFα inhibitors have less severe disease and are less likely to develop disseminated histoplasmosis when compared with organ transplantation or AIDS patients.[5] In this series, only 2 of 5 patients with ocular inflammation who were taking TNFα inhibitors developed disseminated histoplasmosis. Presumably, the patients taking TNFα inhibitors with pulmonary histoplasmosis had weak granulomas that were partially able to contain the organisms and prevent disseminated disease. Although the TNFα inhibitors suppress TNF in different manners, there was no significant difference in severity of histoplasmosis infection in this study; 2 patients were taking adalimumab and 3 were taking infliximab, and 1 from each group had disseminated histoplasmosis.

In this series, the average time from initiation of systemic IMT to diagnosis of histoplasmosis infection was 1.9 years, with a range from 6 months to 16 years, and more than half of the patients (5/9) were taking TNFα inhibitors. Olson and associates reported similar findings in patients with rheumatoid arthritis: the average time to diagnosis of histoplasmosis was 15 months, and 15 of 26 patients were taking TNF inhibitors, although only 5 of 15 had disseminated histoplasmosis.[6]

It is known that patients with disseminated histoplasmosis may have developed reactivation of previously latent fungal organisms in the setting of immunocompromise.[17] In this series, both of the patients with disseminated histoplasmosis had lived in areas endemic for *Histoplasma*, but the duration of time between initiation of systemic IMT and diagnosis of histoplasmosis (10 months and 16 years) suggests that the infections were newly acquired. Despite the potential risk of reactivating latent disease, there are currently no data to suggest that patients should be screened for exposure to *Histoplasma* before starting systemic IMT, in contrast to the guideline stipulating testing for latent tuberculosis before starting a TNFα inhibitor. The absence of a *Histoplasma* screening guideline reflects the difficulty of identifying who is truly at risk for fungal reactivation because ≤80% of the population in an edemic region might show evidence of exposure, yet disseminated histoplasmosis is rare. The low rate of disseminated histoplasmosis among ocular inflammation patients in this series suggests that prescreening is not warranted.

It is notable that among the ocular inflammation patients with symptomatic pulmonary histoplasmosis who were treated (5/7 cases), all were successfully treated with oral antifungal medications alone and did not require intravenous amphotericin. Four of 7 patients (cases 1, 2, 3, and 6) were able to continue systemic IMT for uveitis. Of the other 3 pulmonary histoplasmosis cases, 1 patient (case 7) was still taking methotrexate after infliximab was discontinued and did not develop recurrent uveitis. In another patient (case 8), it was determined that the diagnosis of uveitis was incorrect, so systemic IMT was not restarted for the ocular disease. The third patient (case 9) initially developed recurrent uveitis after stopping methotrexate and infliximab. Subsequently, she was diagnosed with common variable immunodeficiency and intravenous immunoglobulin infusions were initiated with improvement in the uveitis activity. It is possible that undiagnosed common variable immunodeficiency could have influenced her risk of histoplasmosis.

Both of the ocular inflammation patients with disseminated histoplasmosis were initially treated with intravenous amphotericin and subsequently transitioned to oral antifungal agents. In 1 patient (case 5), infliximab was delayed but not discontinued because of the severity of the underlying inflammatory disease (Behçet disease), and indefinite treatment with an antifungal was planned. In the other patient (case 4), methotrexate and adalimumab were immediately stopped, but oral prednisone was continued. When scleritis and uveitic macular edema recurred, mycophenolate mofetil was added. Because of the inability to taper oral prednisone to low doses, adalimumab was restarted 11 months after the diagnosis of disseminated histoplasmosis. Although a 12-month course of antifungal treatment was initially planned, with the reintroduction of adalimumab, it is likely that the patient will remain on antifungal treatment indefinitely.

In general, if the uveitis has been well-controlled without significant ocular morbidity, it may be appropriate to decrease or discontinue systemic IMT; however, in this series, systemic IMT was completely discontinued in only 1 case, and in 3 cases (all pulmonary) the pre-existing systemic IMT regimen was unchanged after histoplasmosis diagnosis. In 3 other cases (1 disseminated), all systemic IMT except prednisone was discontinued, but 2 of these

patients subsequently required addition of other systemic corticosteroid-sparing medications. Among the 5 patients receiving TNFα inhibitors, the medication was continued in only 1 patient, but another later required restart of the TNFα inhibitor because of recurrent ocular inflammation. Overall, there were no deaths and no recurrences of histoplasmosis, including in the 2 patients who remained on or restarted TNFα inhibitors.

As illustrated by the cases in this series, the diagnosis and treatment of histoplasmosis requires close communication and cooperation between ophthalmologists and colleagues in rheumatology and infectious diseases. If there is a previous history of severe ocular inflammatory disease or significant recurrent inflammation, it may be possible to continue or restart systemic IMT, including TNFα inhibitors, as long as the patient's histoplasmosis disease stabilizes and responds to antifungal treatment. In the case of disseminated histoplasmosis, indefinite treatment with systemic antifungals may be required as long as the patient remains on systemic IMT.

This study is limited inherently by its design as a retrospective cohort study. Because of the retrospective design, the histoplasmosis diagnostic criteria were not standardized, but all patients were evaluated by infectious diseases specialists, and therefore we included 1 patient whose diagnosis was not confirmed by the detection of *Histoplasma* in a tissue specimen. We also included 2 ocular inflammation patients with asymptomatic pulmonary histoplasmosis who were not treated with antifungal medications. The clinician should not use these cases as the sole example to guide decisions about continuing systemic IMT for ocular inflammation. It is notable that 4 of the patients had concurrent systemic inflammatory diseases as well as ocular inflammation; in these cases, the decisions to change systemic IMT may have been influenced by morbidity associated with the systemic disease. This single-center study involved a patient population primarily from Minnesota and nearby states, so the results might not be generalizable to other regions. Because of the scope of the database, we were not able to accurately identify the total number of ocular inflammation patients taking systemic IMT to use as the denominator to assess relative risk of histoplasmosis infection. The design of the study also limited the type and extent of statistical analyses. The study set to identify the development of systemic histoplasmosis after IMT and the control cohort was comprised of patients who did not develop systemic histoplasmosis, and therefore no direct comparison regarding incidence or hazard ratio could be calculated.

CONCLUSIONS

IN THIS RETROSPECTIVE SINGLE-CENTER STUDY, 9 CASES OF histoplasmosis developed in patients who were receiving systemic IMT for ocular inflammation. There did not appear to be a relationship between legnth of IMT and the risk of systemic histoplasmosis. All 7 of the patients with symptomatic histoplasmosis had fevers and abnormal chest imaging studies. Five of the patients were receiving TNFα inhibitors, including both cases of disseminated histoplasmosis. Systemic IMT was completely discontinued in only 1 patient. No patients died, and there were no recurrences of histoplasmosis, although ocular inflammation increased in some cases. While systemic IMT is a risk factor, histoplasmosis infection seems to be a rare complication in ocular inflammation patients. With prompt diagnosis and treatment, the prognosis for recovering from the infection is good, and it may not be necessary to discontinue systemic IMT for ocular inflammation—although indefinite antifungal medication may be required. Nonetheless, ophthalmologists who follow ocular inflammation patients should have a low threshhold for investigating new systemic symptoms that are concerning for infectious complications, particularly if TNFα inhibitors are involved and the patient may have been exposed to *Histoplasma*. Close comanagement with rheumatologists and infectious diseases specialists is also paramount.

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