Recognition, Diagnosis, and Treatment of Histoplasmosis Complicating Tumor Necrosis Factor Blocker Therapy

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Life-threatening histoplasmosis is one of the most common opportunistic infections in patients receiving tumor necrosis factor (TNF) blockers. Delays in considering the diagnosis may lead to increased morbidity and mortality. Most affected patients present with pneumonitis, usually accompanied by additional signs of progressive dissemination, or with signs of progressive dissemination alone. The diagnosis often can be promptly established using antigen detection or direct examination of bronchoalveolar lavage specimens. If histoplasmosis is diagnosed promptly, antifungal therapy is highly effective. After a favorable clinical response, the safety of both discontinuation of antifungal therapy and the resumption of TNF blocker remains undetermined. The management of the immune reconstitution inflammatory syndrome that may follow discontinuation of TNF blockers also requires investigation. Prescribers should become aware of the recognition, diagnosis, and treatment of histoplasmosis and educate recipients about decreasing their risk of exposure and both recognizing and reporting signs of early infection.

Histoplasmosis is 3-fold more common than tuberculosis as a cause of serious infection in patients who are receiving tumor necrosis factor (TNF) blockers [1] and is the most frequent invasive fungal infection in such patients, resulting in a mortality rate of 20% [2]. The United States Food and Drug Administration (FDA) has urged healthcare professionals to be alert to the risk for histoplasmosis, because delay in treatment may increase the risk of a life-threatening or fatal outcome [3]. In 21 of 240 cases reported to the FDA, the diagnosis was delayed, and 12 (57%) of the 21 patients died [3]. A tragic fatal case in a young woman in whom histoplasmosis was unsuspected during 12 days of hospitalization before her death [4] underscores the need for education of doctors and patients. We summarize our experience and review the recognition, diagnosis, treatment, and means for reducing the risk of acquiring histoplasmosis.

PATHOGENESIS

TNF plays a critical role in the host's immune response to *Histoplasma capsulatum* [5]. In experimental infection, TNF blockade prevented development of a protective immune response [6–10] by impairing the activation of macrophages [11]. The incidence is higher in patients who are receiving anti-TNF monoclonal antibodies (infliximab or adalimumab) than in those who are receiving soluble-TNF receptor (etanercept) [12]. Potential reasons for this difference may include the broader range of action of the monoclonal antibodies, which block both soluble and cell-associated TNF, including monomeric and trimeric forms. In contrast, etanercept blocks only trimeric soluble TNF [10]. Additional differences include induction of apoptosis of monocytes and T cells by the monoclonal antibodies [13]. This, too, contrasts with etanercept, which is antiapoptotic. Furthermore, infliximab and adalimumab but not etanercept induce complement-mediated lysis of cells that express TNF-α surface receptors, including monocytes. However, other factors may influence the risk of histoplasmosis [10].

Although reactivation of latent infection often is suspected in patients with calcified lesions in the lung or spleen, reexposure, perhaps inoculum dependent, may also be operant, because immunosuppression may have impaired the protective immunity that was induced by prior exposure. If reactivation predominates, the incidence should far exceed the observed

rate of 1–2 cases per 10,000 population [12], because more than half of adults from areas of endemicity exhibit skin test hypersensitivity to histoplasmin, a marker for past histoplasmosis [12, 14]. Additional evidence against reactivation as the principal mechanism is found in a report of nearly 600 transplant patients in Indianapolis, where 3 large outbreaks occurred during the preceding 20 years. Despite many of these patients having radiographic and/or serologic evidence of past histoplasmosis [15], none developed active histoplasmosis. Similarly, in another region of high endemicity among >600 children who were receiving chemotherapy for malignancy, none developed histoplasmosis [16]. In our local experience, of 469 adult patients treated with TNF blockers for inflammatory bowel disease from 2000 through early 2009, only 3 (0.64%) developed histoplasmosis, a frequency similar to that in patients who had undergone organ transplantation at this institution before the 3 outbreaks (0.5%) [17].

Reasons for the rarity of reactivation have not been established but probably include the effectiveness of cellular immunity in killing the pathogen. In support of this hypothesis is a study of 105 consecutive autopsies in a region of high endemicity [18], in which calcified pulmonary granulomas were found to contain yeast forms that resembled *H. capsulatum* in 70 patients (67%). In 40 cases, the granulomas both were cultured for fungus and were injected into mice. All culture results were negative, and none of the mice developed histoplasmosis, leading the authors to conclude that the yeast-like forms were nonviable and that there was "no argument for the existence of endogenous reinfection in histoplasmosis" [18, p. F1]. Whether *H. capsulatum* contained within noncalcified granulomas could remain viable and later reactivate is unknown; however, cultures of such lesions rarely have positive results (Wheat, unpublished observation). Although reactivation of organisms in calcified lesions seems unlikely, TNF blockade may permit a more recently acquired infection to progress by impairing the development of protective granulomas [19]. This may have serious consequences if active histoplasmosis is misdiagnosed as an autoimmune inflammatory disorder and treatment is begun with a TNF blocker [20]. Determining the respective roles of reactivation versus reinfection requires additional investigation.

CLINICAL MANIFESTATIONS

Of the first 10 published cases of histoplasmosis among patients who were receiving TNF blockers, 9 patients required intensive care unit management and 1 died [21]. To date, 88 cases of histoplasmosis have been reported [4, 20, 22–32], the majority from areas in which histoplasmosis is endemic. Of these cases, clinical details were provided in 21. Pneumonia and/or progressive disseminated histoplasmosis (PDH) were present in 70%–80% of cases [4, 20, 22–28].

At the Indiana University Medical Campus (Indianapolis), 19 patients (5 children and 14 adults) have been diagnosed with histoplasmosis while receiving TNF blockers from 2000 through early 2009. Most were receiving additional immunosuppressive agents: methotrexate in 8, azathioprine in 4, corticosteroids in 3, and 6-mercaptopurine in 1. Seventeen patients (89%) presented with progressive febrile illnesses consistent with PDH. Pulmonary involvement was present in 15 patients (79%) and was a prominent feature in 13 (68%). Thirteen cases occurred in patients who were receiving infliximab, 3 in patients who were receiving etanercept, and 3 in patients who were receiving adalimumab. Fifteen patients (79%) required hospitalization, including 4 (21%) who developed respiratory failure and shock. All 19 patients recovered from the infection.

The clinical symptoms of histoplasmosis are nonspecific and require a high index of suspicion for early diagnosis. In regions nonendemic for histoplasmosis, a careful history is needed to determine whether the patient previously lived in or recently traveled to an area of endemicity [33]. A prolonged, worsening febrile illness or an undiagnosed pneumonia should alert the physician to consider the diagnosis of histoplasmosis. Proof of the diagnosis of PDH may be difficult, however. A proven diagnosis requires demonstration of organisms in extrapulmonary specimens and usually requires invasive procedures. Confirmation of PDH could delay diagnosis by 1–4 weeks or could lead to failure to make the diagnosis if those tests results are negative. In this report, such confirmation occurred in only 3 patients (16%). Accordingly, in most cases the diagnosis of PDH is based on other findings, including hepatosplenomegaly, extrapulmonary lymphadenopathy, compatible oral or skin lesions, adrenal or intestinal masses, gastrointestinal obstruction or bleeding, or endoscopic demonstration of gastrointestinal lesions. Laboratory parameters that suggest PDH include anemia, leukopenia, thrombocytopenia, hepatic enzyme elevation, and/or adrenal insufficiency. Miliary or diffuse reticulonodular pulmonary infiltrates also suggest dissemination in immunosuppressed patients [34]. In some cases, PDH may initially present with only prolonged fever and weight loss.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Current recommendations call for the discontinuation of TNF blockers in patients with findings that are suggestive of systemic fungal infection [3]. In such instances, we have observed paradoxical clinical worsening despite documenting improvement of the fungal infection. These features are compatible with immune reconstitution inflammatory syndrome (IRIS). The pathogenesis of IRIS has been investigated in tuberculosis and appears to be caused by an "explosion of…Th1-responses," including pathogen specific interferon-γ production and nonspecific TNF-α production [35, p. 738]. IRIS has been observed

Table 1. Clinical and Laboratory Findings in Patients with Histoplasmosis Complicating Tumor Necrosis Factor (TNF) Blocker Therapy

No.[a]	Age in years, sex	Anti-TNF	Duration[b]	Other meds	Disease[c]	Ser	Cult	Path	Ant	Exposure[d]
1	66, F	Inflix	3 mo	Azathio	Sarcoidosis	ND	Neg	BAL, TBBx	8.49 U	No
2	46, M	Adali	4 mo	Methot	RA	Pos	Neg	Liver Bx	5.55 U	Yes
3	50, F	Inflix	Unk	None	RA	Pos	BAL	BAL,TBBx	20.66 U	No
4	8, F	Etan	< 1 mo	Methot	JRA	Neg	ND	ND	5.08 ng/mL	Yes
5	10, F	Etan	4 mo	None	JRA	Pos	ND	ND	1.4 U	No
6	57, M	Inflix	Unk	Methot	Psoriasis	Pos	ND	ND	[f]Neg	Yes
7	17, F	Inflix	9 mo	Azathio, pred	JRA	Pos	Neg	Neg	4.3 U	Yes
8	13, F	Inflix	1 yr	None	JRA/psoriasis	Pos	Neg	Neg	27.27 U	Yes
9	16, M	Inflix	9 mo	Methot	Uveitis	Pos	Neg	ND	11.2 U	Yes
10	50, M	Inflix	10 wk	methot, pred	RA	Pos	BAL	BAL	12.3 U	No
11	60, F	Inflix	7 mo	MP	Crohn	Pos	Blood	BAL, bone marrow	>39.0 ng/mL	No
12	46, F	Inflix	3 yr	Azathio	Crohn	Pos	Neg	Neg	4.6 U	No
13	50, F	Etan	Unk	Methot	RA	Pos	ND	ND	3.1 U	Yes
14	22, F	Inflix	3 mo	Azathio	Crohn	Neg	Neg	Neg	5.72 ng/mL	Yes
15	52, M	Adali	Unk	Unk	RA	ND	Unk	Unk	28.97 U	
16	34, F	Inflix	2.5 yr	Methot	RA	Neg	Neg	BAL, TBBX	3.0 ng/mL	No
17	32, F	Inflix	> 3 yr	None	Crohn	Pos	ND	ND	3.26 ng/mL	No
18	43, F	Inflix	3 yr	Methot	Psoriasis	Pos	Blood, BAL	BAL	16.12 ng/mL	Yes
19	28, F	Adali	3 mo	None	Crohn	ND	Neg	ND	10.3 ng/mL	No

NOTE. ABLC, amphotericin B lipid complex; adali, adalimumab; AMB, amphotericin B; ant, *Histoplasma* antigen; azathio, azathioprine; BAL, bronchoalveolar lavage; bilat, bilateral; Bx, biopsy; cult, culture; etan, etanercept; fluc, fluconazole; FUO, fever of unknown origin; inflix, infliximab; IRIS, immune reconstitution inflammatory syndrome; itra, itraconazole; JRA, juvenile rheumatoid arthritis; L-AMB, liposomal amphotericin B; meds, medicines; methot, methotrexate; MP, mercaptopurine; neg, negative; path, pathology; PDH, progressive disseminated histoplasmosis; pos, positive; pred, prednisone; RA, rheumatoid arthritis; ser, serology; TBBx, transbronchial biopsy; unk, unknown; vori, voriconazole; X, present.

[a] Patient identifier.

[b] Duration of treatment with TNF blocker at the onset of symptoms of histoplasmosis.

[c] Condition for which TNF blocker was prescribed.

[d] History of or probable exposure to *Histoplasma capsulatum*.

[e] Clinical severity of histoplasmosis (severe: hypotension, respiratory failure, intensive care unit admission; moderate: hospitalization for amphotericin B treatment; or mild: outpatient azole treatment.

[f] Antigen was detected after ultrafiltration of the urine (<0.6 ng/mL) [37] and edetic acid (EDTA)–heat treatment of the serum (1.74 ng/mL) [38], and the patient had received ketoconazole or itraconazole for 4 wks before testing.

[g] Patient 18 improved after 4 mo of a planned course of ⩾6 mo of itraconazole.

[h] Patient 19 was recently diagnosed and started a 12-mo course of itraconazole. Only 3 mo of follow-up data are available at this point.

in patients with tuberculosis after discontinuation of TNF blockers [36]. In our patients, the occurrence of IRIS after stopping TNF blockers was considered to be a potential cause for clinical deterioration in 8 (42%) of the 19 patients; 2 cases are presented below.

The first case involved a 66-year-old woman with sarcoidosis who presented with diffuse pneumonia. Chest computed tomography (CT) showed bilateral septal thickening and interstitial reticulonodular infiltrates; the diagnosis was made by the demonstration of granulomas containing yeast forms compatible with *H. capsulatum* in bronchoalveolar lavage (BAL) and transbronchial biopsies (case 1 in tables 1 and 2). *Histoplasma* antigen was 8.49 U in the urine. Amphotericin B therapy was begun, and the azathioprine dose was reduced to 50 mg twice a day. Seven days later (10 weeks after the last dose of infliximab) and after an initial improvement accompanied by de-

crease of the *Histoplasma* antigen to 4.9 U, respiratory distress requiring mechanical ventilation developed. The chest CT now showed diffuse airspace disease, and lung biopsy showed diffuse alveolar damage and nonnecrotizing granulomas containing yeast forms; culture results were negative. Amphotericin B was continued, and corticosteroids were administered. She recovered during a 40-day hospitalization. Although progression of histoplasmosis could have accounted for the clinical worsening, persistence of negative culture results, decreasing antigen concentration, and clinical improvement following the administration of corticosteroids suggest IRIS.

The second patient was a 60-year-old woman who presented with a progressive illness that culminated in high fever, pancytopenia, hyperbilirubinemia, and elevated hepatic enzymes. These symptoms were followed by the onset of septic shock and respiratory failure 10 weeks after the last dose of infliximab.

Table 1. *(Continued.)*

Clinical	PDH	Severity[e]	IRIS	AMB	Azole	Anti-TNF restarted	Outcome
FUO, lobar pneumonia	X	Severe	Pos	AMB 12 d	Unk	No	Recovered, no follow-up
FUO, bilat pneumonia	X	Moderate	Pos	None	Vori 2 wk; fluc 1 mo; Itra 9 mo	No	Recovered, no relapse methot/pred
Bilat pneumonia	X	Moderate	Neg	None	Itra 12 mo	No	Recovered, no relapse, 1 yr
Bilat pneumonia	X	Moderate	Pos	L-AMB 1 wk	Itra 3 mo	Yes	Recovered, 3 yr
Fever	X	Moderate	Neg	ABLC 11 d	Itra 6 mo	No	Recovered, 4 yr
Lobar pneumonia	X	Mild	Neg	None	Itra 12 mo	No	Recovered, 1 yr
Fever	X	Moderate	Neg	AMB 5 wk	Itra 5 mo	Yes	Recovered, 8 yr
FUO, bilat pneumonia	X	Moderate	Neg	ABLC 2 wk	Itra 12 mo	Yes	Recovered, 5 yr
Lobar pneumonia	X	Moderate	Neg	ABLC 3 wk	Itra 11 mo	No	Recovered, 14 mo
Pneumonia	X	Severe	Pos	AMB 1 wk	Itra 12 mo	Yes	Recovered, 7 yr
Bilat pneumonia, hemophagocytosis	X	Severe	Pos	AMB, L-AMB; 4 wk	Itra 12 mo	No	Recovered , 5 mo
Lung mass, chest pain	No	Moderate	Pos	None	Itra 12 mo	Yes	Recovered, 3 yr
Pneumonia	No	Moderate	Neg	None	Itra 12 mo	Yes	Recovered, 7 yr
Bilat pneumonia	X	Moderate	Pos	AMB 1 wk	Itra 14 mo	No	Recovered, 18 mo
Lobar pneumonia	X	Moderate	Unk	Unk	Unk	No	Recovered, 3 yr
Diffuse pneumonia	X	Moderate	Neg	L-AMB 10 d	Itra 12 mo	No	Recovered, 4 mo
Diffuse pneumonia	X	Mild	Neg	None	Itra 24 wk	Yes	Recovered, 11 mo
Diffuse pneumonia	X	Severe	Neg	L-AMB 20 d	Itra	No	Recovered, 4 mo[g]
Fever	X	Moderate	Pos	None	Itra	No	Recovered, 3 mo[h]

A bone marrow biopsy showed hypocellularity, reactive histiocytosis with hemophagocytic activity, and intracellular yeast-like forms compatible with *H. capsulatum*, a constellation of findings consistent with the reactive hemophagocytic syndrome [39, 40]. The *Histoplasma* antigen was >39 ng/mL in the urine, and cultures of blood grew *H. capsulatum.* Amphotericin B and corticosteroids were started, and the patient recovered after a prolonged and complicated hospitalization. Although these findings could indicate progression of histoplasmosis, an alternative possibility is that they represent "unmasking" of histoplasmosis at the nadir of the TNF blocker effect, as described in patients with AIDS after they start antiretroviral therapy [41]. A similar course was described in the recent report of the young woman with undiagnosed and untreated histoplasmosis, in whom a rapidly progressive illness culminated in multiorgan failure and death 1 month after her last dose of adalimumab [4]. Among our cases, findings compatible with IRIS have included respiratory failure [22], findings compatible with reactive hemophagocytic syndrome [39, 40], liver dysfunction and abdominal pain, splenic lesions, and chest pain accompanied by enlargement and necrosis of mediastinal lymph nodes. Other studies have reported additional manifestations, such as bowel perforation [20] and skin and soft-tissue necrosis [23, 24]. Note that the authors of these reports did not attribute their patients' findings to IRIS.

Paradoxical worsening may be misinterpreted as a sign of treatment failure, an incorrect diagnosis of histoplasmosis, or another infection, thereby resulting in unneeded testing and alterations of therapy [42]. Although clinical worsening may sometimes represent progressive infection, IRIS should be considered as an alternative possibility. In the face of clinical deterioration following initial improvement in response to antifungal therapy, factors that favor the occurrence of IRIS, in order of their significance, include decreasing antigen concentrations, failure to improve despite the use of the most effective antifungal regimen, and sustained improvement following the addition of corticosteroid therapy. Reversion of culture results to negative would also favor IRIS, but the delay for isolation of the fungus reduces the value of culture in making treatment decisions. Further research is needed to assess the role of IRIS in patients with histoplasmosis complicating TNF blocker therapy.

SCREENING FOR RISK OF HISTOPLASMOSIS

Education of patients and physicians is essential for the prevention and management of histoplasmosis before beginning TNF blockers. Patients should be asked about potential exposure with specific reference to high-risk activities in regions of endemicity (Table 3) or symptoms of active or recent histoplasmosis. In such instances, a chest radiograph is recommended before beginning TNF blockers. A careful travel history also is needed in patients who reside in areas nonendemic for

Table 2. Clinical Findings of Paradoxical Worsening in Patients with Histoplasmosis Complicating Tumor Necrosis Factor (TNF) Blocker Therapy

No.[a]	TNF blocker		Antifungal		IRIS manifestation	Culture or antigen	Modification of therapy	Outcome
	Drug	Duration[b]	Drug	Duration[c]				
1	Inflix	10 wk	AMB	7 d	ARDS, reticulonodular infiltrates → bilateral consolidation	8.48 U → 4.39 U at IRIS	Corticosteroid	Recovered after 40 d hospitalization
2	Adali	6 wk	Vori	33 d	Worsening liver functions	5.55 U → 1.77 U at IRIS	Vori changed to fluc	Recovered
4	Etan	1 wk	L-AMB	4 d	Worsening respiratory failure, requiring high flow O_2	5.08 ng/mL → <0.6 ng/mL at IRIS	None	Recovered
10	Inflix	4 wk	AMB	6 d	ARDS, reticulonodular infiltrates → bilateral consolidation	BAL cult positive at presentation → negative at IRIS, path pos at both times	None	Recovered after 6 wk of mechanical ventilation
11	Inflix	10 wk	AMB or L-AMB	1 d	ARDS, reactive hemophagocytic syndrome	BAL & bone marrow pos	Corticosteroid & L-AMB	Recovered after 12 d of mechanical ventilation and 40 d hospitalization
12	Inflix	9 wk	Itra	0	Enlarging lung mass and hilar lymphadenopathy	FNA of lymph node showed reactive inflammation, Ag 4.6 U	Corticosteroid	Recovered
14	Inflix	6 wk	Itra	6 d	ARDS, reticulonodular infiltrates → bilateral consolidation	5.72 ng/mL → 5.21 ng/mL at IRIS	Itra changed to AMB	Recovered after 1 wk mechanical ventilation and 20 d hospitalization
19	Adali	4 wk	Itra	12 d	New left upper quadrant abdominal pain with left shoulder referred pain, new low density splenic lesions, hilar lymphadenopathy and pulmonary nodules on CT scan	10.3 ng/mL → 4.29 ng/mL	None	Recovered

NOTE. Ag, silver; AMB, amphotericin B; BAL, bronchoalveolar lavage; CT, computed tomography; cult, culture; etan, etanercept; fluc, fluconazole; FNA, fine needle aspiration; inflix, infliximab; IRIS, immune reconstitution inflammatory syndrome; itra, itraconazole; L-AMB, liposomal amphotericin B; path, pathology; pos, positive; vori, voriconazole.

[a] Patient identifier.

[b] Duration after stopping TNF inhibitor at onset of possible IRIS.

[c] Duration of antifungal therapy at onset of possible IRIS.

histoplasmosis. Radiographic abnormalities associated with active histoplasmosis may include diffuse reticulonodular or miliary infiltrates, focal or patchy infiltrates, noncalcified pulmonary nodules, and/or hilar or mediastinal lymphadenopathy. Calcified nodules, lymph nodes, or splenic lesions suggest past infection and may not represent a risk for active histoplasmosis. In the absence of factors suggestive of recent exposure, active histoplasmosis, or histoplasmosis within the previous 2 years, routine screening with chest radiographs is not recommended.

Routine screening for antibodies to *H. capsulatum* or for *Histoplasma* antigen also is not recommended. We examined this approach in children who were beginning treatment with TNF blockers for rheumatologic disorders from October 2003 through December 2005. Anti-*Histoplasma* antibody titers and antigenuria were measured in 23 patients before initiating TNF

blockers and thereafter at intervals of 1–3 months. Histoplasmosis was diagnosed in 2 of the 23 patients; however, each had negative serologic and antigen tests before diagnosis. The first patient (Table 1, case 9) had negative results for serologic tests (complement fixation and immunodiffusion) and *Histoplasma* antigen tests before starting infliximab. Thereafter, 8 *Histoplasma* antigen tests at monthly intervals had negative results. Five weeks later, he reported fever, and histoplasmosis was confirmed with a *Histoplasma* antigen of 11.2 U and a complement fixation antibody titer of 1:256. The second patient (Table 1, case 5) had negative results for serologic and antigen tests before treatment with etanercept. Four months later, she developed fever and was diagnosed with histoplasmosis with a positive antigen of 1.4 U, serologic conversion with a complement fixation titer of 1:256, and positive H and M bands by immu-

Table 3. Advice to Patients about Histoplasmosis

Before starting TNF blocker, tell your doctor about

1. Possible exposure to *Histoplasma* via the following sites (activities):

   Old buildings (demolition, remodeling, cleaning)

   Chicken coops (demolition, cleaning, fertilizer)

   Bird roosts (excavation, camping, cutting wood)

   Wood piles (transporting or burning wood)

   Caves (spelunking)

2. Recent travel to an area of endemicity[1]

3. Past diagnosis of histoplasmosis

4. Pneumonia in past 2 years

5. Any symptoms in past 3 months[2]

During TNF blocker therapy,

1. Avoid exposure to *Histoplasma*

2. Tell your doctor about possible exposure and recent travel[1]

3. Tell your doctor about any new symptoms

4. Don't put off contacting your doctor

NOTE. TNF, tumor necrosis factor.

[1] Areas of endemicity include parts of the Midwestern United States, Mexico, Central and South America, Africa, and Asia.

[2] Common symptoms include prolonged/unexplained fever, sweats, cough, fatigue, and weight loss. Other symptoms include headaches, skin or mouth sores, abdominal pain, diarrhea, and blood in the bowel movements. Note that this is not a complete list of symptoms of histoplasmosis, so tell your doctor about all of your symptoms.

nodiffusion. Screening for antibody also has not identified patients at risk for reactivation of histoplasmosis in solid organ or bone marrow transplant recipients [15]. Our findings do not support a role for routine screening with serologic tests or antigen detection.

DIAGNOSIS

In symptomatic patients, evaluation in all patients should include ⩾2 fungal blood cultures, tests for *Histoplasma* antigenuria and antigenemia, and serologic testing. Fungal cultures were performed in 12 of our patients and had positive results in 4 (33%). Antigenuria was detected in 18 (95%) of 19 patients, with the MVista *Histoplasma* antigen assay [43]. Although antigenuria was undetectable in 1 patient, antigenemia was detected after edetic acid (EDTA) and heat treatment [38] and antigenuria was detected after ultrafiltration [37]. That patient had received antifungal therapy for 1 month before antigen testing was performed, perhaps causing antigen levels to decrease below the detection limit of the assay. Thus, antigenemia and/or antigenuria were present in all 19 patients. The EDTA-heat treatment of serum was implemented routinely in 2009, but ultrafiltration of urine remains investigational.

If bronchoscopy is performed, BAL and biopsy specimens should be cultured and examined microscopically with appropriate methods to identify fungal pathogens. BAL should also be tested for antigen [44]. Results of cytopathologic exami-

nation were positive in BAL specimens in 6 of 8 patients, culture in 3 of 8, and antigen in all 4 patients for whom testing was performed.

Biopsy of other sites also should be considered if antigen test results are negative. Direct examination of mucosal or skin lesions may yield a prompt diagnosis. Examination of bone marrow may be useful if anemia, leukopenia, or thrombocytopenia is present. In severe cases, intracellular yeast may be seen in Wright-stained blood smears [4].

Serologic tests that use immunodiffusion and complement fixation methods may be useful when other test results are negative [45]. Serology test results were positive in 14 (82%) of 17 patients and were the sole laboratory basis for diagnosis in 1 patient (Table 1, case 6). Note that immunodiffusion tests that demonstrate only M precipitins and complement fixation titers of 1:8 or 1:16 may be seen in past histoplasmosis and thus may not reflect active infection [45].

ANTIFUNGAL TREATMENT

Antifungal treatment is indicated for all patients [46]. Consultation with a physician experienced in the diagnosis and management of histoplasmosis is encouraged [3], especially in severe cases. Empirical treatment with antifungal agents should be considered while awaiting results of diagnostic tests for patients with compatible epidemiologic and clinical features. A lipid formulation of amphotericin B is recommended for hospitalized adults; children may be treated with amphotericin B deoxycholate [46]. Itraconazole may be used to complete the course of therapy. In patients with mild manifestations, itraconazole is recommended. Treatment should be continued for ⩾12 months and until clinical findings have resolved, antigenemia has cleared, and antigenuria has decreased to <4 ng/mL. Antigen concentration should be monitored for ⩾1 year after completion of therapy and for evaluation of suspected relapse [46]. In our series, an amphotericin B formulation was given to 11 patients for a mean of 15.6 days (median, 12 days; standard deviation [SD], 3.3 days; range, 7–35 days). Itraconazole was given to all patients for a mean of 11 months (median, 12 months; SD, 4.6 months; range, 3–24 months) and was the sole therapy in 6 patients.

The role of suppressive antifungal therapy to prevent relapse is uncertain [46]. If TNF blockers are resumed or immunosuppression is intensified, patients should be monitored more closely. Increasing antigen levels are strongly suggestive of relapse or reexposure and require careful clinical and laboratory evaluation, and reinstitution of antifungal therapy should be considered if relapse is likely.

Some experts recommend that TNF blockers not be resumed. In our series, the TNF blockers were given again in 7 patients, all of whom had completed a mean of 10 months of antifungal therapy (range, 6–12 months) and 3 of whom continued treat-

ment with itraconazole. None have experienced a relapse during follow-up of 1–8 years.

MANAGEMENT OF IMMUNOSUPPRESSION AND IRIS

Discontinuation of the TNF blocker was suggested in the FDA alert [3] and by the manufacturers. Whether doing so increases the risk for IRIS is unknown. The recommended therapy for IRIS is administration of corticosteroids [47], but TNF blockers also have been used [48, 49].

The underlying inflammatory disease may worsen when the TNF blocker is stopped, necessitating resumption of immunosuppressive therapy. Patients should be monitored for relapse of histoplasmosis, especially if they are no longer receiving antifungal therapy. Remaining uncertainties with respect to the management of immunosuppressive medications and treatment of IRIS can best be answered with a prospective trial.

PREVENTION

Patients who are receiving TNF blockers should be educated about their risk for acquiring histoplasmosis, types of environmental foci likely to be contaminated with *H. capsulatum,* activities to avoid, and symptoms for which they should seek medical attention. General guidance is provided in Table 3.

Antifungal prophylaxis is not recommended for patients living in areas of endemicity who are receiving TNF blockers. However, in the setting of an outbreak in which the attack rate exceeds 10 cases per 100 patient-years, prophylaxis should be considered [46]. Prophylaxis should be continued while the attack rate exceeds this threshold.

If a patient was diagnosed with histoplasmosis during the 2 years preceding TNF blocker therapy, or if the clinical, radiographic, or laboratory findings suggest that the patient may have had histoplasmosis during that interval, antifungal therapy may be considered [46]. Evidence for histoplasmosis might include history of a pneumonia associated with antigenuria, antigenemia, or positive serologic test results. In such circumstances, administration of itraconazole for 3 months before starting TNF blocker therapy and for ⩾1 year thereafter should be considered.

Acknowledgments

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