CLINICAL PRACTICE

Clinical Vignette

A Case of Disseminated Histoplasmosis in a Patient with Rheumatoid Arthritis on Abatacept

Nina Jain, MD, MBA, MSc¹, Jeffrey B. Doyon, MD, PhD¹, Jacob E. Lazarus, MD, PhD^{1,2,3}, Inga-Marie Schaefer, MD⁴, Melanie E. Johnncilla, MD⁴, Agoston T. Agoston, MD⁴, Anuj K. Dalal, MD¹, and Gustavo E. Velásquez, MD, MPH^{1,2,5}

¹Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; ²Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA; ³Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA; ⁴Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA; ⁵Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.

Biologic agents are effective treatments for rheumatoid arthritis but are associated with important risks, including severe infections. Tumor Necrosis Factor (TNF) α inhibitors are known to increase the risk of systemic fungal infections such as disseminated histoplasmosis. Abatacept is a biologic agent with a mechanism different from that of TNF α inhibitors: It suppresses cellular immunity by competing for the costimulatory signal on antigen-presenting cells. The risk of disseminated histoplasmosis for patients on abatacept is not known. We report a case of abatacept-associated disseminated histoplasmosis and review the known infectious complications of abatacept. While the safety of resuming biologic agents following treatment for disseminated histoplasmosis is also not known, abatacept is recommended over TNF α inhibitors for rheumatoid arthritis patients with a prior serious infection. We discuss the evidence supporting this recommendation and discuss alternative treatments for rheumatoid arthritis patients with a history of a serious infection.

KEY WORDS: infectious disease; arthritis; drugs.

J Gen Intern Med 33(5):769–72

DOI: 10.1007/s11606-018-4383-0

© Society of General Internal Medicine 2018

Disease-modifying antirheumatic drugs (DMARDs), including methotrexate and biologic agents, reduce joint inflammation and improve functional outcomes in rheumatoid arthritis, but are associated with significant side effects.¹ Biologic agents, in particular Tumor Necrosis Factor (TNF) α inhibitors, increase the risk of severe infections.¹ In 2008, the US Food and Drug Administration (FDA) issued a warning about the increased risk of systemic fungal infections in patients treated with TNF α inhibitors.² The FDA has not issued a similar warning for abatacept, which has a mechanism of immunosuppression that is distinct from TNF α inhibitors. While abatacept

has previously been associated with some fungal infections, only one case of abatacept-associated, non-disseminated histoplasmosis has been reported in the literature to date.³ Here, we report a case of abatacept-associated disseminated histoplasmosis. The patient provided verbal consent for the publication of her case.

CASE

A 62-year-old woman presented to the hospital in autumn 2016 with a 10-day history of abdominal pain, nausea, and fevers. Her medical history was remarkable for asthma and rheumatoid arthritis that had been treated with etanercept for several years. Six months before admission, she was transitioned from etanercept to adalimumab for improved symptom control. Three months before admission, she presented to the clinic with arthralgias and joint stiffness: She was switched to methotrexate and abatacept, and adalimumab was discontinued. She also received a 5-day course of prednisone for an asthma exacerbation in the month prior to admission. She lived in the Dominican Republic before immigrating to the USA in the 1980s. Five weeks after starting abatacept and 7 weeks prior to admission, she visited an underground lagoon in Mexico.

At the time of presentation, she was febrile to 103 °F and appeared markedly uncomfortable. Her abdomen was distended and diffusely tender without rebound tenderness or guarding. Her musculoskeletal exam was unremarkable. Her complete blood count, basic metabolic panel, and total bilirubin were normal. Liver enzymes were ALT 146 U/L, AST 298 U/L, and alkaline phosphatase 338 U/L. An abdominal CT scan was normal.

Throughout her hospitalization, her abdominal pain and fevers continued. Blood cultures were repeatedly negative. AST and ALT remained stably elevated while alkaline phosphatase peaked at 776 U/L, with direct hyperbilirubinemia to 1.6 mg/dL. Viral hepatitis serologies and serum PCR testing for Epstein Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), *Babesia*, and *Ehrlichia/Anaplasma* were unrevealing. Antibody tests for Human Immunodeficiency Virus (HIV) and Lyme disease were negative. An interferon gamma release assay for

Received June 2, 2017

Revised September 25, 2017

Accepted February 21, 2018

Published online March 12, 2018

tuberculosis was negative. Serum 1,3-beta-D-glucan, a nonspecific test for fungal infections, was elevated to 126 pg/mL, and galactomannan, a test for *Aspergillus*, was normal. The elevated beta-D-glucan increased our suspicion for a fungal process.

MRI of the abdomen was obtained to rule out an infectious process not visualized on CT, and to evaluate the liver given her rising alkaline phosphatase and bilirubin. The study revealed splenomegaly with innumerable T2 hypointense lesions with delayed contrast enhancement, and hepatomegaly with marked periportal edema. Repeat 1,3-beta-D-glucan, obtained 4 days after the initial result, was elevated further at 237 pg/mL. A liver biopsy demonstrated multiple non-necrotizing granulomas with multinucleated giant cells. Budding yeast forms in the center of the granulomas, consistent with *Histoplasma capsulatum*, were identified by silver stain (Fig. 1). Urine and serum *Histoplasma* antigens, which were pending at the time of liver biopsy, returned positive at 16 ng/mL (with ≥ 0.5 ng/mL being positive) and elevated beyond the measurement of the assay, respectively. CNS infection was excluded by lumbar puncture.

A diagnosis of disseminated histoplasmosis was made on the ninth day of her admission, and she was started on liposomal amphotericin B. Methotrexate and abatacept were discontinued. She was transitioned to itraconazole after 8 days of amphotericin treatment, because of worsening renal function, and discharged after a 19-day hospitalization. Five months after discharge, her symptoms completely resolved, yet urine and serum *Histoplasma* antigens remained positive. She continued on itraconazole and remained off biologic agents. Periodic rheumatoid arthritis flares were treated with oral corticosteroids, except for one severe flare 10 months after diagnosis, which resulted in restarting methotrexate. Her rheumatologists have not excluded reinitiating abatacept in the future.

DISCUSSION

Histoplasmosis is a fungal infection caused by inhalation of *Histoplasma capsulatum* microconidia, which are endemic to the Ohio and Mississippi River valleys in the USA, Central America, and parts of southern Europe, Asia, and Africa.⁴ Bird and bat guano supports the growth of *Histoplasma*; disruption of contaminated soil and exposure in caves in endemic areas can lead to infection.⁴ Infections in immunocompetent individuals are often asymptomatic. Disseminated histoplasmosis presents in patients who are unable to mount an effective cell-mediated immune response to *Histoplasma*, including those with advanced HIV, hematologic malignancies, solid organ transplant recipients, and patients on immunomodulatory biologic agents, such as TNF α inhibitors.

Abatacept is a commonly used immunosuppressive biologic agent with a mechanism of action distinct from TNF α inhibitors, and with an unknown risk of disseminated histoplasmosis. Abatacept inhibits T cell activation by competing for the costimulatory signal on antigen-presenting cells (APCs). Complete T cell activation requires an interaction between

costimulatory molecules CD80 or CD86 on APCs and CD28 on T cells. Cytotoxic T lymphocyte antigen 4 (CTLA4) is an inhibitory signal on the surface of T cells with a stronger affinity for CD80 and CD86 than CD28. CTLA4 can inhibit complete T cell activation by competing for costimulatory signals. Abatacept is a recombinant fusion protein including the extracellular domain of CTLA4.⁵ By inhibiting full T cell activation, abatacept prevents the production of cytokines important to the progression of rheumatoid arthritis but also to killing intracellular organisms, such as *Histoplasma*.

The patient in this case report was diagnosed with disseminated histoplasmosis that was associated with the use of abatacept. To our knowledge, treatment with abatacept has not been previously reported as a risk factor for disseminated histoplasmosis. Long-term prednisone use poses an infectious risk; however, our patient only received a 5-day course of prednisone prior to symptom onset. Although disseminated histoplasmosis in patients on methotrexate alone has been reported,⁶ a systematic review including 106 trials found that standard-dose biological agents carried a higher risk of serious infection compared to methotrexate.⁷ It is possible that the patient's prior use of TNF α inhibitors may have contributed to her susceptibility to disseminated disease. The half-life of adalimumab is 10–20 days,⁸ and her presumptive exposure to *Histoplasma* in Mexico occurred 5 weeks, approximately two half-lives, after discontinuing adalimumab. Although residual immune suppression from adalimumab may have contributed, treatment with full-dose abatacept is a more likely explanation for the development of disseminated histoplasmosis in this case.

The patient's travel to an underground lagoon in Mexico 1 month prior to symptom onset is highly suggestive of primary infection. Given that the patient previously lived in the Dominican Republic where *Histoplasma* is endemic, reactivation cannot be excluded as the cause of the patient's presentation. However, reactivation would have been more probable during the period when the patient was treated with TNF α inhibitors, which unlike abatacept have a well-characterized association with disseminated histoplasmosis.² More generally, reactivation is not favored as the mechanism of histoplasmosis infections in patients on TNF α inhibitors.⁹

Impaired cellular immunity by abatacept can lead to infectious complications other than histoplasmosis, albeit at a low rate. A 2008 integrated safety analysis of patients on abatacept demonstrated that the incidence of serious infections was slightly higher in patients on abatacept as compared to placebo (3.47 vs. 2.41 events/100 person-years).¹⁰ Opportunistic infections occurring in these patients included tuberculosis (0.06 events/100 person-years), aspergillosis (0.02), blastomycosis (0.01) and systemic candidal infection (0.01).¹⁰ By comparison, TNF α inhibitors are associated with a risk of tuberculosis of 0.15 and 0.09 events/100 person-years for infliximab and adalimumab, respectively.¹¹ Although the rates of these systemic infections on abatacept are low, the increased risk and severity of the illnesses suggest clinicians should be aware of the possibility of these conditions in patients on abatacept.

Figure 1 Multiple non-necrotizing granulomas with multinucleated giant cells are identified in the patient's liver (a, $\times 20$ and b, $\times 40$, hematoxylin and eosin stain). Methenamine silver staining highlights budding yeast forms in the center of the granulomas, which are consistent with *Histoplasma capsulatum* (c, $\times 40$, and d, $\times 100$, arrows).

Subsequent studies have questioned the risk of serious infections in patients taking abatacept. A 2009 meta-analysis including five placebo-controlled trials in patients taking abatacept observed common infections including pulmonary infections, bacteremias, and gastrointestinal infections. However, there was no significant increase in the rate of serious infections, defined as life-threatening infections requiring intravenous antibiotics or hospitalization, with abatacept treatment compared to placebo.¹² A single case of pulmonary aspergillosis and one case of unconfirmed tuberculosis were reported.¹² Although the risk of tuberculosis appears low in patients taking abatacept, screening for latent tuberculosis is recommended when initiating this medication.¹³

The evidence indicating whether it is safe to resume biologic agents during or after treatment for histoplasmosis is scant. In a case series of seven patients treated for histoplasmosis, no patients relapsed after TNF α inhibitors were resumed (follow-up period 1–8 years).⁹ However, three of these patients were maintained on itraconazole during the follow-up period. The Infectious Diseases Society of America (IDSA) recommends itraconazole treatment until clinical and laboratory findings normalize.¹⁴ Since 10–15% of patients with disseminated histoplasmosis relapse, lifelong itraconazole therapy may be necessary for patients who require continued immunosuppressive therapy.¹⁴ Per IDSA, patients diagnosed with active histoplasmosis up to 2 years prior to initiating

immunosuppression may require itraconazole prophylaxis, but the duration of prophylaxis needed is not clear.¹⁴

The safety of restarting biologic agents after a serious infection is contingent not only on the patient's immune status, but also the nature of the initial infection. For instance, it has been shown that it is safe to resume TNF α inhibitor treatment following completion of an antituberculous regimen.¹⁵ Immunosuppressed individuals infected with histoplasmosis can relapse without reexposure.⁴ For this reason, providers should proceed with caution when considering the continuation of biologic agents in patients treated for histoplasmosis.

For rheumatoid arthritis patients with a prior serious infection, the American College of Rheumatology conditionally recommends abatacept over TNF α inhibitors.¹⁶ This recommendation is based on a single comparative study of biologic therapies used after a serious infection in patients treated with TNF α inhibitors.¹⁷ The study found that patients taking abatacept after their initial infection were less likely to be re-hospitalized for a subsequent infection compared to patients taking infliximab.¹⁷ Although this finding indicates abatacept may be a safer alternative to other biologic therapies for rheumatoid arthritis, our case demonstrates that providers should remain alert for possible serious fungal infections on this medication.

When deciding to restart an immunosuppressive agent in the setting of a serious infection, the potential side effects of the immunosuppressive agents must be balanced against those

of the antibiotics. In addition to increased risk for serious infection, patients on abatacept had higher rates of autoimmune adverse events, most commonly psoriasis and vasculitis, when compared to patients given placebo.¹⁸ Patients on abatacept had similar rates of malignancy as patients given placebo, but compared to the US general population, patients taking abatacept had higher rates of lymphoma.¹⁸ Methotrexate is frequently associated with hepatic and gastrointestinal toxicity, and long-term prednisone can lead to Cushing's syndrome, osteoporosis, and an increased risk of cardiovascular disease.^{19–21} Itraconazole, which our patient will take long term, is generally well-tolerated and most commonly causes gastrointestinal side effects.²² Accordingly, determining which agent to choose when restarting immunosuppression requires weighing the severity of rheumatoid arthritis symptoms, concern for a relapse of histoplasmosis, and the side effect profiles of various available DMARDs and antibiotics.

Patients taking immunomodulating medications may be at risk for serious fungal infections, including histoplasmosis, and this disease should be considered in patients on TNF α inhibitors or abatacept who present with fever of unknown origin. Gathering a comprehensive travel history to evaluate for proximate travel to endemic areas is particularly important, as recent exposure is the likely cause of histoplasmosis for patients on these medications. The safety of resuming biologic agents following successful treatment of the infection should be evaluated on a case-by-case basis.

Corresponding Author: Gustavo E. Velásquez, MD, MPH; Department of Global Health and Social Medicine Harvard Medical School, Boston, MA, USA (e-mail: gvelasquez@bwh.harvard.edu).

Funding Information This work was supported by the National Institute of Allergy and Infectious Diseases (grant number L30 AI120170 to G. E. V.). G. E. V. also received support from the Ronda Stryker and William Johnston Fellowship in Global Health and Social Medicine and the Dr. Lynne Reid/Dr. Eleanor and Miles Shore Fellowship at Harvard Medical School, the Burke Global Health Fellowship at the Harvard Global Health Institute, and the AIDS Clinical Trials Group Minority HIV Investigator Mentoring Program.

Compliance with Ethical Standards:

Conflict of Interest: The authors have no conflicts of interest to report.

REFERENCES

1. Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;51 Suppl 5:v38–47. <https://doi.org/10.1093/rheumatology/kes114>.
2. Food and Drug Administration. Postmarket drug safety information for patients and providers—information for healthcare professionals: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm>. Accessed 7 Dec 2016.
3. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis*. 2014;73(1):86–94. <https://doi.org/10.1136/annrheumdis-2013-203843>.
4. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev*. 2007;20(1):115–132. <https://doi.org/10.1128/CMR.00027-06>.
5. Genovese MC, Becker J-C, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N Engl J Med*. 2005;353(11):1114–1123. <https://doi.org/10.1056/NEJMoa050524>.
6. LeMense GP, Sahn SA. Opportunistic infection during treatment with low dose methotrexate. *Am J Respir Crit Care Med*. 1994;150:258–260.
7. Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet*. 2015;386(9990):258–265. [https://doi.org/10.1016/S0140-6736\(14\)61704-9](https://doi.org/10.1016/S0140-6736(14)61704-9).
8. Bang LM, Keating GM. A review of its use in rheumatoid arthritis. *Biodrugs*. 2004;18(2):121–139.
9. Hage CA, Bowyer S, Tarvin SE, Helper D, Kleiman MB, Wheat LJ. Recognition, diagnosis, and treatment of histoplasmosis complicating tumor necrosis factor blocker therapy. *Clin Infect Dis*. 2010;50(1):85–92. <https://doi.org/10.1086/648724>.
10. Schiff M. Abatacept treatment for rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50(3):437–449. <https://doi.org/10.1093/rheumatology/keq287>.
11. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DPM. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2006;54(8):2368–2376. <https://doi.org/10.1002/art.21978>.
12. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis*. 2009;68(1):25–32. <https://doi.org/10.1136/ard.2007.083188>.
13. FDA Approved Drug Products: BLA 125118. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125118s209lbl.pdf. Accessed 27 Dec 2017.
14. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the infectious diseases society of America. *Clin Infect Dis*. 2007;45(7):807–825. <https://doi.org/10.1086/521259>.
15. Denis B, Lefort A, Flipo RM, et al. Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)- α antagonist therapy: safe re-initiation of TNF- α blockers after appropriate anti-tuberculous treatment. *Clin Microbiol Infect*. 2008;14(2):183–186. <https://doi.org/10.1111/j.1469-0691.2007.01891.x>.
16. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1–26. <https://doi.org/10.1002/art.39480>.
17. Yun H, Xie F, Delzell E, et al. Risk of hospitalized infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. *Ann Rheum Dis*. 2015;74(6):1065–1071. <https://doi.org/10.1136/annrheumdis-2013-204011>.
18. Weinblatt ME, Moreland LW, Westhovens R, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol*. 2013;40(6):787–797. <https://doi.org/10.3899/jrheum.120906>.
19. Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(5):423–426. <https://doi.org/10.1136/ard.62.5.423>.
20. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. *Lancet*. 2001;357(9258):783–791. [https://doi.org/10.1016/S0140-6736\(00\)04172-6](https://doi.org/10.1016/S0140-6736(00)04172-6).
21. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med*. 1994;96(2):115–123. [https://doi.org/10.1016/0002-9343\(94\)90131-7](https://doi.org/10.1016/0002-9343(94)90131-7).
22. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients: a multicenter, randomized trial. *Ann Intern Med*. 2003;138(9):705. <https://doi.org/10.7326/0003-4819-138-9-200305060-00006>.