

Pulmonary Cryptococcosis in the Setting of Tofacitinib Therapy for Psoriasis

Lucia Seminario-Vidal MD PhD, Wendy Cantrell DNP, and Boni E. Elewski MD
Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL

ABSTRACT

Tofacitinib is a novel drug that inhibits the JAK-STAT signaling pathway. It has been approved for the treatment of psoriatic arthritis and it is under investigation for the treatment of psoriasis and other inflammatory disorders. We report a case of pulmonary cryptococcosis in an otherwise immunocompetent patient taking tofacitinib for psoriasis. We hypothesized that tofacitinib contributed to this infection through inhibition of cytokines required for differentiation of T cells and suppression of macrophage activation. As dermatologists begin to use this drug they should be aware of the potential for cryptococcocal infection, because delay of diagnosis may increase the risk of a life-threatening outcome.

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CASE REPORT

A 65 year-old Caucasian man with severe plaque psoriasis and psoriatic arthritis presented with a ten week history of progressive nasal congestion, intermittent fever, non-productive cough, and dyspnea. He was receiving tofacitinib for 6 months as investigational treatment for psoriasis and was pleased with the medication because his skin was clear, and he had no joint pain. At initial presentation of his respiratory symptoms, he went to an urgent care facility, where he was diagnosed with presumed influenza and was treated with oseltamivir. Three weeks after, his symptoms had not improved. His primary care physician treated him with levofloxacin and fluticasone, as well as salmeterol inhalation powder for 10 days. Two weeks later, he was treated with ceftriaxone and prednisone 10 mg oral daily for 7 days. He reported worsening of his symptoms during the treatments. The patient was HIV negative, without history of immunodeficiency disorder, or malignancy. He had no history of tuberculosis exposure and a Quantiferon-TB Gold was negative prior to initiation of tofacitininb therapy. He denied smoking, drinking, using illicit drugs, or travelling.

On exam, he was in mild distress, with low-grade fever, and oxygen saturation of 93% on room air. His neck was not stiff, skin and joints were normal, and lung sounds were diminished on the right. Laboratory studies revealed normal serum chemistries and complete blood cell counts. Chest radiography demonstrated multifocal right-sided pneumonia. Serum cryptococcal antigen was positive, with a titer of 1:1024. No confirmatory fungal culture was obtained. A lumbar puncture was negative.

Tofacitinib was discontinued and he received oral fluconazole 400 mg daily for 6 months, showing a quick recovery. Cryptococcal serum titers were negative at the end of the treatment. Infectious disease recommended that he may restart a biologic while on prophylactic fluconazole 200 mg weekly. However, the patient refused biologic or systemic therapy for his psoriasis. His psoriasis has been treated with phototherapy achieving a partial control.

Infection with *Cryptococcus* usually results in harmless colonization of the airways. An effective immune response can eliminate the yeast or result in the formation of dormant yeasts within a pulmonary lymph node. If the cell-mediated immunity is defective, e.g., in patients receiving high dose glucorticoid therapy,[1] dormant yeasts may reactivate causing pneumonia, meningitis, or disseminated disease. No reports have yet described an association of cryptococcosis with tofacitinib therapy for psoriasis.

Tofacitinib is a novel oral Janus kinase (JAK) inhibitor in development for the treatment of several inflammatory diseases. It has recently demonstrated efficacy and safety in phase 2 trials for moderate-to-severe plaque psoriasis.[2] While no serious infections were observed in this study population, they were noted in patients with rheumatoid arthritis.[3] In vitro and in vivo studies support a potential predisposition for fungal infections with tofacitinib therapy. It interferes with JAK-STAT signaling, blocking cytokines required for the differentiation of Th2 and Th1 cells,[4] and suppresses the activation of blood-derived macrophages.[5] Clinically, cryptococcal pneumonia has been reported in one Australian patient with rheumatoid arthritis taking tofacitininb 10 mg twice a day and sulfasalazine 1 g twice

a day of for approximately 8 months.[6] The patient had several comorbidities that could have contributed to disease development including diabetes mellitus type 2, diverticulitis, allergic rhinitis, hypertension, hypercholesterolemia, sleep apnea, hepatic steatosis, dry eyes, and Ross river virus.[6]

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Pulmonary cryptococcosis can occur in immunocompetent or immunocompromised individuals. It has been reported in 10% to 40% of patients with no apparent immunodeficiency.[7] As is the case with most immunocompetent patients who develop symptomatic pulmonary cryptococcosis, our patient likely developed a primary infection that remained latent until his cell-mediated immunity was suppressed with tofacitinib and corticosteroids. This case illustrates that it is crucial to monitor for the subtle symptoms of cryptococcocal infection in the setting of tofacitinib therapy because delay of diagnosis may increase the risk of a life-threatening outcome.

DISCLOSURES

Dr. Seminario-Vidal has no conflicts of interest. Dr. Elewski is in the advisory board and an investigator for Novartis and Pfizer, and an investigator for Janssen, Merck, Lilly, Amgen and Abbvie. Dr. Cantrell has been an investigator for Pfizer Inc.

REFERENCES

1. Bratton EW, El Husseini N, Chastain CA, et al. Comparison and Temporal Trends of Three Groups with Cryptococcosis: HIV-Infected, Solid Organ Transplant, and HIV-Negative/Non-Transplant. *PLoS One*. 2012;7
2. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol*. 2012;167:668-77.
3. Fleishman R, Kremer J, Cush John, et al. Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis. *N Engl J Med*. 2012; 367: 495-507.
4. Yarilina A, Xu K, Chan C, et al. Regulation of inflammatory responses in tumor necrosis factor-activated and rheumatoid arthritis synovial macrophages by JAK inhibitors. *Arthritis Rheum*. 2012;64:3856-66.
5. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol*. 2011;186: 4234-43.
6. Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2013;159: 253-61.
7. Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis*. 2001;33:690-9.

AUTHOR CORRESPONDENCE

Boni E. Elewski MD
E-mail:..... belewski@uabmc.edu