An Opportunistic Infection Associated With Ruxolitinib, a Novel Janus Kinase 1,2 Inhibitor

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We report a case of *Cryptococcus neoformans* pneumonia in a patient taking ruxolitinib, a janus kinase 1,2 inhibitor approved for the treatment of myelofibrosis. We hypothesize that ruxolitinib contributed to this infection through its effects on cell-mediated immunity. Clinicians should be aware of the potential for intracellular or opportunistic infections associated with this novel drug class.

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Abbreviations: JAK = janus kinase; TNF- α = tumor necrosis factor- α

A 66-year-old man with a 12-year history of polycythemia vera and myelofibrosis was referred to the pulmonary clinic because of a 6-week history of dyspnea, cough, and intermittent fever (temperature, 101°F). His cough was initially productive of brownish sputum but later became nonproductive and was associated with progressive fatigue and dyspnea on exertion.

The patient completed several courses of oral antibiotics with no improvement in symptoms. In addition, he had been taking a stable dose of prednisone 5 mg daily for bone pain and constitutional symptoms of myelofibrosis since before initiation of ruxolitinib (Jakafi; Incyte Corporation). Three days prior to his presentation, the prednisone was increased to 40 mg daily, with minimal improvement in symptoms.

Ruxolitinib was originally initiated because of splenomegaly and constitutional symptoms. The patient had been receiving therapy for 18 months following enrollment in

a phase 3 trial. He is retired and lives in rural southern Oregon. He reported no exposure to tobacco, dust, birds, or other animals. His mother had TB when he was a child, but his tuberculin skin test was negative prior to initiation of ruxolitinib.

On examination, the patient was afebrile; BP was 110/68 mm Hg; pulse, 94/min; respiratory rate, 16/min; and oxygen saturation, 96% on room air. His cardiopulmonary and neurologic examinations were normal. There were no rashes noted.

Laboratory investigations revealed mild leukocytosis ($13.3 \times 10^3/\text{mL}$ with 93% neutrophils, without immature neutrophils [bands]). Otherwise, his CBC count and serum chemistry findings were normal. Noncontrast chest CT scan demonstrated multifocal consolidations with surrounding ground glass opacities in a bronchovascular distribution and with upper-lobe predominance (Fig 1). Fiber-optic bronchoscopy with BAL grew *Cryptococcus neoformans* on fungal culture. *Cryptococcus gattii* was excluded using canavanine-sulfate, glycine, bromothymol blue agar. Serum cryptococcal antigen titer results were positive (1:4). A lumbar puncture revealed no WBCs, no organisms on Gram stain, normal protein and glucose levels, and negative results for cryptococcal antigen.

The *C neoformans* was sensitive to fluconazole in vitro. The patient was treated with fluconazole 400 mg po daily following a single loading dose of 800 mg po. After 3 weeks of therapy, he noticed improvement in his cough and resolution of his fever. Ruxolitinib was later discontinued because of thrombocytopenia, which likely was a consequence of fluconazole inhibiting hepatic metabolism of ruxolitinib. The patient self-discontinued fluconazole after

FIGURE 1. Noncontrast CT image of the chest demonstrating multifocal consolidations with surrounding ground glass opacities in a bronchovascular distribution and upper-lobe predominance.

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5 months of therapy because of perceived side effects, after which he was restarted on ruxolitinib with improvement in his myelofibrosis symptoms.

DISCUSSION

C neoformans is an encapsulated fungus found in soil and is associated with bird droppings, especially pigeons. As an intracellular pathogen, cell-mediated immunity is essential in controlling cryptococcal infections. Although *C neoformans* can rarely infect immunocompetent hosts (usually in association with heavy exposure), it is considered an opportunistic pathogen because infections occur primarily in patients with profound impairments in cell-mediated immunity. Patients with myelofibrosis can be considered relatively immunocompromised, but opportunistic infections are rare, especially among patients such as the one presented here with preserved leukocyte counts. We found no previous reports in the medical literature of cryptococcal or other opportunistic infections in association with myelofibrosis alone.

Ruxolitinib is an inhibitor of janus kinase (JAK) 1,2, which was recently approved by the US Food and Drug Administration for treatment of myelofibrosis. This drug has demonstrated efficacy in reducing the symptom burden of myelofibrosis and may have a survival benefit.¹ JAK 1,2 inhibitors are currently being studied for broader use in a variety of conditions, including polycythemia vera, essential thrombocytosis, acute myelogenous leukemia, psoriasis, rheumatoid arthritis, and inflammatory bowel disease.^{2,3}

The postulated therapeutic mechanism of ruxolitinib is downregulation of multiple cytokines responsible for the constitutional symptoms of myelofibrosis, including IL-1, IL-6, and tumor necrosis factor- α (TNF- α).⁴ TNF- α plays an essential role in controlling intracellular pathogens like *Cryptococcus* primarily through immunoregulatory mechanisms involving CD-4, CD-8, and natural killer cells.⁵ The importance of TNF- α was demonstrated in postmarketing experience with TNF- α inhibitors, which became associated with reactivation TB and other opportunistic infections, including *Cryptococcus*.⁶

Although the prescribing information for ruxolitinib describes a higher rate of herpes zoster in the treatment arm, cell-mediated immune suppression has not been reported as an adverse effect from clinical trial experience.

The patient had other impairments of his immune system, including low-dose steroid exposure, but we hypothesize that ruxolitinib played an important role in his immune dysfunction and the development of *C neoformans* pneumonia.

More real-world experience with ruxolitinib may establish impairment of cellular immunity and an associated risk of opportunistic infections with this novel drug class. Although case reports and associations cannot prove causation, immune suppression is a biologically plausible consequence of JAK inhibition. As JAK inhibitors gain broader application, clinicians should be aware of the potential for immune suppression and opportunistic infection so that with early recognition, they may prevent significant patient morbidity and mortality.

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REFERENCES

1. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.
2. Garber K. Pfizer's JAK inhibitor sails through phase 3 in rheumatoid arthritis. *Nat Biotechnol*. 2011;29(6):467-468.
3. Sandborn WJ, Ghosh S, Panes J, et al; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med*. 2012;367(7):616-624.
4. Tefferi A. Challenges facing JAK inhibitor therapy for myeloproliferative neoplasms. *N Engl J Med*. 2012;366(9):844-846.
5. Voelz K, May RC. Cryptococcal interactions with the host immune system. *Eukaryot Cell*. 2010;9(6):835-846.
6. Salmon-Ceron D, Tubach F, Lortholary O, et al; RATIO group. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis*. 2011;70(4):616-623.