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Letter to the Editor

Cryptococcal immune reconstitution syndrome in HIV-negative patients

I read with interest the case report by Narayanan et al.[1] on cryptococcal immune reconstitution inflammatory syndrome (IRIS) during steroid withdrawal. Corticosteroids are known to depress the host response by suppression of the inflammatory response. Treatment with corticosteroids has been shown to be the common underlying condition predisposing to cryptococcosis in non-HIV-infected patients.[2–5] We also had a patient at our institution who, after treatment with prednisone for nephrotic syndrome for 2 years, developed cryptococcal meningitis. Prednisone was discontinued after she was diagnosed. After 4 weeks of amphotericin B combined with flucytosine therapy, the patient's symptoms (fever, headache, vomiting, blindness) improved significantly; her cerebrospinal fluid pressure decreased from 400 mmH_2O to 180 mmH_2O and cryptococcal antigen titer declined from 1:256 to 1:32. However, on day 40 of treatment her condition deteriorated rapidly, manifested as headache, vomiting, sepsis syndrome with sterile cultures, cerebrospinal fluid pleocytosis, increasing intracranial pressure, and cultures that were negative for *Cryptococcus neoformans*. All this was not explained by any newly acquired infection. We suspected IRIS, but the patient was discharged because of the family's refusal to continue therapy.

IRIS is characterized by a paradoxical worsening of treated opportunistic infections due to the recovery of the immune system when factors promoting immunosuppression or inhibiting inflammation are rapidly decreased or removed. IRIS is now well-recognized among HIV-infected patients, and several diagnostic criteria for a case definition have already been published.[6] Clinicians most commonly pay attention to the HIV-infected patients who initiate antiretroviral therapy or to transplant recipients reducing their immunosuppression therapy. IRIS is also seen in other immunocompromised hosts, but there is insufficient data about this entity in non-HIV-infected patients.[1,7–9] The concept of IRIS in HIV-negative patients and its diagnosis in the context of opportunistic mycoses remains poorly characterized for healthcare providers. In the case reported by Narayanan et al.[1] and in our case, both patients underwent a rapid reduction or withdrawal of steroids after diagnosis of cryptococcosis, and received an effective antifungal therapy. Both antimicrobial use and rapid reduction or withdrawal of immunosuppressive agents might predispose to the development of IRIS in solid organ transplant recipients.[10] Hypercalcemia associated with granulomatous inflammatory reactions may play an important role in the diagnosis of this condition. But without a description and established diagnostic criteria for non-HIV-infected patients, IRIS is easily construed as a failure of therapy or a relapse caused by the patient's inability to eliminate the pathogens, leading to unwarranted or inappropriate changes in treatment. Diagnosis and management of IRIS in non-HIV-infected patients poses great challenges for care providers, so more clinical investigations are needed to support a definitive conclusion.

Conflict of interest: No conflict of interest to declare.

References

1. Narayanan S, Banerjee C, Holt PA. Cryptococcal immune reconstitution syndrome during steroid withdrawal treated with hydroxychloroquine. *Int J Infect Dis* 2011;**15**:e70–3.
2. Baddley JW, Perfect JR, Oster RA, Larsen RA, Pankey GA, Henderson H, et al. Pulmonary cryptococcosis in patients without HIV infection: factors associated with disseminated disease. *Eur J Clin Microbiol Infect Dis* 2008;**27**:937–43.
3. Kiertiburanakul S, Wirojtananugoon S, Pracharktam R, Sungkanuparph S. Cryptococcosis in human immunodeficiency virus-negative patients. *Int J Infect Dis* 2006;**10**:72–8.
4. 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.
5. Zhu LP, Wu JQ, Xu B, Ou XT, Zhang QQ, Weng XH. Cryptococcal meningitis in non-HIV-infected patients in a Chinese tertiary care hospital, 1997-2007. *Med Mycol* 2010;**48**:570–9.
6. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;**10**:251–61.
7. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, et al. An immune reconstitution syndrome-like illness associated with *Cryptococcus neoformans* infection in organ transplant recipients. *Clin Infect Dis* 2005;**40**:1756–61.
8. Cheng VC, Yuen KY, Wong SS, Woo PC, Ho PL, Lee R, et al. Immunorestitution diseases in patients not infected with HIV. *Eur J Clin Microbiol Infect Dis* 2001;**20**:402–6.
9. Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. *Curr Opin Infect Dis* 2009;**22**:394–402.
10. Singh N, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. *Clin Infect Dis* 2008;**47**:1321–7.

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