Mycopathologia (2018) 183:495–498
https://doi.org/10.1007/s11046-017-0230-9

OPINION PAPER

Opinion: Paracoccidioidomycosis and HIV Immune Recovery Inflammatory Syndrome

Renata Buccheri · Gil Benard

Received: 25 September 2017 / Accepted: 16 November 2017 / Published online: 20 November 2017

Abstract Two distinct patterns of immune recovery inflammatory syndrome (IRIS) are recognized, paradoxical and unmasking IRIS. Here we raise some concerns regarding the first case of neuroPCM-IRIS published to date, as recently proposed by Almeida and Roza (Mycopathologia 177:137–141, 2017) for a patient originally described by Silva-Vergara et al. (Mycopathologia 182:393–396, 2014), taking in account the different case definitions for IRIS and the cases of neuroparacoccidioidomycosis already described in the literature. We are concerned that data from the case report have been misinterpreted and that no regard has been given to the possibility that the development of manifestations of neuroPCM after starting antiretroviral therapy and antifungal treatments could represent the predicted course of a missed neuroPCM diagnosis at presentation whose treatment failed. We hypothesize that diagnosis of the neuroPCM would not have been missed if careful screening for opportunistic infection of the central nervous system was performed prior to antiretroviral therapy initiation. Currently, there is no definitive diagnostic test for IRIS and diagnostic suspicion, as well as its management, are based on image studies and non-specific clinical signs and symptoms of inflammation. IRIS remains a diagnosis of exclusion, after considering drug toxicity, microbiologic treatment failure and the expected course of newly or previously diagnosed opportunistic infections.

Keywords Paradoxical IRIS · Unmasking IRIS · Paracoccidioidomycosis · HIV

R. Buccheri
Instituto de Infectologia Emílio Ribas, São Paulo, Brazil

R. Buccheri (✉)
Laboratory of Medical Investigation Unit #53, Medical School and Tropical Medicine Institute, University of São Paulo Medical School, Avenida Doutor Arnaldo, 455. Cerqueira Cesar, São Paulo, SP, Brazil
e-mail: renatabuccheri@gmail.com

G. Benard
Laboratories of Medical Investigation Units #53 and #56, Medical School and Tropical Medicine Institute, University of São Paulo Medical School, Avenida Doutor Arnaldo 455, São Paulo, SP, Brazil

Currently, two distinct patterns of immune recovery inflammatory syndrome (IRIS) are recognized, paradoxical and unmasking IRIS. Paradoxical IRIS is the term used to describe immune recovery-related inflammatory phenomena following initiation of antiretroviral therapy (ART) that leads to a paradoxical worsening of symptoms in patients on treatment for an opportunistic infection (OI). The syndrome is usually a consequence of exaggerated activation of the immune system by persistent antigens of nonviable pathogens; therefore, pathogens should not be cultured from affected body sites [1]. Specifically regarding paradoxical IRIS associated with opportunistic

mycoses, evidence from the literature proposes as diagnostic criteria the worsening or appearance of new clinical and/or radiological manifestations consistent with an inflammatory process occurring during appropriate antifungal therapy with sterile cultures for the initial fungal pathogen within 12 months of ART initiation [2, 3]. On the other hand, unmasking IRIS denotes an occult opportunistic disease that was not apparent at the time of ART initiation but becomes clinically manifest as a result of ART-induced immune recovery. In such cases, viable pathogens may be isolated from samples obtained from affected body sites. Most cases of IRIS are expected to occur within the first few months of the initiating ART [1].

The case report by Silva-Vergara et al. published in 2014 describes a naive HIV-infected patient with severe immunocompromise and a 3-month history of respiratory symptoms documented by thoracic computerized tomography (CT). Transbronchial biopsy revealed fungal structures consistent with *Paracoccidioides* spp. Treatment with amphotericin B (Ampho B) for a week followed by itraconazole for paracoccidioidomycosis (PCM) and ART was initiated. The patient evolved with improved clinical status and viral suppression associated with decrease in HIV viral load and increase in TCD4 cell count. However, 9 months later he was readmitted with neurological symptoms and the magnetic resonance imaging (MRI) of the brain disclosed a hypointense oval lesion with mild perilesional edema on the right internal capsule. Cerebrospinal fluid (CSF) evaluation showed a mild increase in cellularity (12 cells/dl) and protein (109 mg/dl) with normal glucose value. Direct mycological examination showed the presence of yeast cells typical of *Paracoccidioides* spp.; culture of the CSF grew *Paracoccidioides* spp. The chest X-ray was normal. Treatment with itraconazole was replaced by trimethoprim–sulfamethoxazole (TMT-SMZ) followed by Ampho B during 1 year and until complete radiological improvement in the central nervous system (CNS) lesion [4]. On their paper published October 2016, Almeida and Roza [5] on reviewing the case report suggested that IRIS should be considered during the clinical course of the patient. Unfortunately, no consideration has been given to the timing of ART and distinction between paradoxical and unmasking forms of IRIS. This would be the first case of PCM-IRIS published to date.

Considering the different published case definitions for IRIS [6–8], we are concerned that data from the case report may have been misinterpreted by Almeida and Roza and that no regard has been given to the possibility that the development of manifestations of neuroPCM after starting ART and antifungal treatment could represent the predicted course of a CNS infection that did not respond to treatment/whose treatment failed.

We believe that, to provide a thoughtful interpretation of the case report, we should consider all the possible reasons why the patient presented CNS symptoms and radiological impairment after 9 months of the initial diagnosis of PCM.

First, the presence of microbiologically active lesion strongly contradicts the diagnosis of paradoxical-neuroPCM-IRIS. Second, this diagnosis could not be established with certainty because neither the initial neuroimaging of the CNS nor the characteristics of the initial CSF were provided, precluding characterization of an immune response recovery-related CNS deterioration.

The presence of *Paracoccidioides* yeast cells in CSF is an uncommon finding [9], as is the growth of *Paracoccidioides* spp. from cultures of patients' specimens who are under proper antifungal therapy. Both findings strongly suggest failure of the antifungal (itraconazole) therapy. In fact, this drug is not recommended to treat CNS lesions due to *Paracoccidioides* spp. [10], which, together with its interaction with the nonnucleoside reverse transcriptase inhibitor (efavirenz), known to reduce itraconazole serum levels [11], favors the hypothesis of emergence of manifestations of an initially subclinical CNS involvement that was inappropriately treated.

With respect to unmasking IRIS, its case definition is more controversial than that of paradoxical IRIS because this entity may be difficult to distinguish from either the development of an OI in a patient who is still immunocompromised at the initial phase of ART or the expected clinical progression of an OI that was missed at presentation [12]. The characteristic course of events in unmasking IRIS involves a new diagnosis of an OI during the early phase of ART presenting clinical features of an excessive inflammatory response. According to some authors, the challenge is to differentiate between an OI with typical manifestations of the illness from an atypical presentation compatible with unmasking IRIS [7, 13].

The present case also does not fit the clinical case definition of unmasking IRIS because the severely immunocompromised patient was on treatment for a recognized OI that appeared before initiation of ART. We suggest that neuroPCM was already present when PCM was diagnosed. We hypothesize that the neuroPCM diagnosis would not have been missed if a careful screening for CNS-OI prior to ART initiation was performed. In fact, patients with HIV/PCM usually present a more severe and disseminated disease with multiple extrapulmonary lesions and unusual involvement of organs such as heart, thyroid and kidneys [9, 14]. Of note, Hutzler et al. [15] performed brain CT of 40 HIV-uninfected PCM patients. Of these, imaging findings compatible with neuroPCM were found in five patients, being two patients asymptomatic, two symptomatic and one patient presented symptoms 3 months after the initial diagnosis due to irregular treatment. More recently, in the largest case series of neuroPCM, neurological symptoms began before the onset of systemic symptoms in 21% of the cases, simultaneously in 33%, and after the systemic symptoms in 46% [9].

Moreover, the initial suboptimal antifungal therapy (whether due to drug–drug interaction or low SNC penetration) may not have prevented the dissemination of the disease or worsening of the CNS lesion. In addition, the primary prophylaxis with TMP-SMX may have delayed the onset of CNS symptoms. It is conceivable to suggest that, had the patient received a full therapeutic TMT-SMZ dose since the beginning of treatment, the CNS involvement would have passed unnoticed.

We recognize the difficulty to discriminate, based on clinical grounds, between the contribution of an exacerbated inflammatory component and the regular presentation and course of an illness. However, knowledge gained from published case series and case reports indicates that the present case did not present any peculiarity that could be attributed to IRIS. Non-HIV-infected patients with neuroPCM present a wide range of clinical manifestations, non-specific CSF findings and brain CT showing the presence of solitary or multiple hypodense lesions with annular or nodular contrast enhancement with perilesional edema and, eventually, hydrocephalus [9, 16, 17]. On the other hand, in the four published HIV-neuroPCM cases (without IRIS), neurological manifestations were symptomatic meningitis [18], severe ocular involvement with a silent CNS lesion [19], ventricular compression on brain CT in a patient with systemic symptoms that arose 5 months before the onset of neurological manifestation [20], and in one patient the disease was asymptomatic and the CSF and brain CT uneventful, the diagnosis being established on autopsy [21]. Overall, these reports reinforce the hypothesis that the patient presented an expected clinical course for an untreated neuroPCM in the context of AIDS during the early phase of ART.

Currently, there is no definitive diagnostic test for IRIS and diagnostic suspicion, as well as its management, are based on image studies and non-specific clinical signs and symptoms of inflammation. IRIS remains a diagnosis of exclusion, after considering drug toxicity, microbiologic treatment failure and the expected course of newly or previously diagnosed OIs [3, 12, 22].

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards There was no research involving human participants or animals.

References

1. French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. Clin Infect Dis. 2009;48:101–7.
2. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis. 2007;7:395–401.
3. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV infected individual: proposed clinical case definitions. Lancet Infect Dis. 2010;10:791–802.
4. Silva-Vergara ML, Rocha IH, Vasconcelos RR, et al. Central nervous system paracoccidioidomycosis in an AIDS patient: case report. Mycopathologia. 2014;177:137–41.
5. de Almeida SM, Roza TH. HIV immune recovery inflammatory syndrome and central nervous system paracoccidiodomycosis. Mycopathologia. 2017;182:393–6.
6. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS. 2004;18:1615–27.
7. Shelburne ISA, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine. 2002;81:213–27.
8. Robertson J, Meier M, Wall J, et al. Immune reconstitution syndrome in HIV: validating a case definition and

identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis. 2006;42:1639–46.
9. de Almeida SM, Queiroz-Telles F, Teive HA, et al. Central nervous system paracoccidioidomycosis: clinical features and laboratorial findings. J Infect. 2004;48:193–8.
10. Shikanai-Yasuda MA, Mendes RP, Colombo AL, et al. Brazilian guidelines for the clinical management of paracoccidioidomycosis. Rev Soc Bras Med Trop. 2017;. https://doi.org/10.1590/0037-8682-0383-2017.
11. Ma Q, Okusanya OO, Smith PF, et al. Pharmacokinetic drug interactions with nonnucleoside reverse transcriptase inhibitors. Expert Opin Drug Metab Toxicol. 2005;1:473–85.
12. Walker NF, Scriven J, Meintjes G, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS. 2015;7:49–64.
13. Davies MA, Meintjes G. Assessing the contribution of the immune reconstitution inflammatory syndrome to mortality in developing country antiretroviral therapy programs. Clin Infect Dis. 2009;49:973–5.
14. Morejón KM, Machado AA, Martinez R. Paracoccidioidomycosis in patients infected with and not infected with human immunodeficiency virus: a case-control study. Am J Trop Med Hyg. 2009;80:359–66.
15. Hutzler RU, Brussi MLP, Capitani CM, et al. Acometimento neurológico da paracoccidioidomicose avaliado pela tomografia computadorizada de crânio [in Portuguese]. Rev Paul Med. 1985;103:243–4.
16. Gasparetto EL, Liu CB, de Carvalho Neto A, et al. Central nervous system paracoccidioidomycosis: imaging findings in 17 cases. J Comput Assist Tomogr. 2003;27:12–7.
17. Pedroso VS, Vilela Mde C, Pedroso ER, et al. Paracoccidioidomycosis compromising the central nervous system: a systematic review of the literature [in Portuguese]. Rev Soc Bras Med Trop. 2009;42:691–7.
18. de Almeida SM, Roza TH, Salvador GLO, et al. Neurological and multiple organ involvement due to *Paracoccidioides brasiliensis* and HIV co-infection diagnosed at autopsy. J Neurovirol. 2017;. https://doi.org/10.1007/s13365-017-0577-1.
19. Finamor LP, Muccioli C, Martins MC, et al. Ocular and central nervous system paracoccidioidomycosis in a pregnant woman with acquired immunodeficiency syndrome. Am J Ophthalmol. 2002;134:456–9.
20. Guimarães JCA, Bortoliero AI, Bonametti AM, et al. Infecção oportunista do sistema nervoso central por Paracoccidioides brasiliensis: relato do caso [abstract no 114]. Rev Soc Bras Med Trop. 1991;24:30–1.
21. Colombo AL, Junior GT, Lotfi CJ et al. Paracoccidioidomicose disseminada em pacientes com AIDS (achado de necropsia) [abstract no 42]. In: Program and abstracts of the 26th congresso da sociedade Brasileira de medicina tropical (São Paulo). São Paulo: Sociedade Brasileira de Medicina Tropical; 1989.
22. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8:516–23.