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REVIEW

The immune reconstitution inflammatory syndrome related to HIV co-infections: a review

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Abstract The immune reconstitution inflammatory syndrome (IRIS) is a consequence of an excessive pathogen-specific immune recovery reaction and occurs in a subset of patients on antiretroviral therapy (ART). Infective forms of IRIS may present either as an 'unmasking' of a previously subclinical infection or the paradoxical clinical deterioration of an infection for which the patient received appropriate antimicrobial therapy. The most important risk factors for IRIS are a low CD4+ T-cell count and a short time between treatment of the infection and the commencement of ART. The general approach to the treatment of IRIS is to continue ART and provide antimicrobial therapy for the provoking infection. The majority of cases are self-limiting; however, mortality and hospitalisation rates are particularly high when tuberculosis- or cryptococcal-IRIS affects the central nervous system (CNS). Corticosteroid therapy should be considered in certain forms of IRIS after the exclusion of other conditions that could explain the inflammatory manifestations in the patients. Given that a low CD4+ T-cell count is a major risk factor for the development of IRIS, commencing ART at a CD4+ T-cell count of >350/μL will prevent most cases.

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Introduction

There has been a marked decline in the frequency of opportunistic infections in human immunodeficiency virus (HIV)-infected patients since the introduction of antiretroviral therapy (ART). This results from a gradual restoration of pathogen-specific immunity, reflected by an increase in the CD4+ T-cell count and a decrease of the HIV viral load. However, a subset of patients starting ART develops a unique clinical syndrome mediated by an overt inflammatory response directed against viable or non-viable organisms and other triggers. This entity is most widely described as the "immune reconstitution inflammatory syndrome" (IRIS), which usually presents as two syndromes; paradoxical IRIS, characterised by the initiation of ART during or after treatment of the infection, or unmasking IRIS, where the infection was not diagnosed before the start of ART [1, 2]. IRIS commonly presents during the initial 3 months of ART, although intervals of less than one week to more than 4 years have been reported [2–4]. In a systematic review of cohort studies, any type of IRIS developed in 16.1% of unselected patients starting ART and death occurred in 4.5% of them [5].

IRIS may also present as non-infectious syndromes, such as Graves' disease and sarcoidosis [6, 7]. In this paper, we will only review IRIS related to infections.

Diagnosis

To date, there is no laboratory test to diagnose or predict IRIS, making it a primarily clinical diagnosis. The exclusion of differential diagnoses such as treatment failure because of antimicrobial resistance or suboptimal drug concentrations, drug reactions and alternative opportunistic conditions is required before making the diagnosis of IRIS. The wide spectrum of clinical manifestations and large range of pathogens able to cause IRIS hampers consensus on the diagnostic criteria for IRIS. The International Network for the Study of HIV-associated IRIS (INSHI) was launched in 2006 to address these issues. Consensus case definitions for tuberculosis (TB) and cryptococcosis-IRIS were formulated and published [2, 8].

Pathogenesis

The pathogenesis of IRIS is not yet fully elucidated, but it is apparent that, during ART, the restoration of protective pathogen-specific immune responses occurs after the initiation of therapy. Patients with low CD4 counts are at high risk of developing IRIS [7]. The immunopathology of IRIS is largely determined by the provoking pathogen. The presence of CD8+ T-lymphocytes predominates in IRIS, which is provoked by viruses such as JC virus and cytomegalovirus (CMV). A T-helper 1 (Th1) response with an increased number of circulating interferon-γ-producing T-cells and Th1-cytokines [9], causing a granulomatous reaction, predominates in IRIS caused by mycobacteria, as well as other intracellular organisms, such as cryptococci, *Histoplasma* and *Leishmania* species [1]. The innate immunity, particularly macrophages, also seems to be involved in mycobacteria-related IRIS [10, 11]. A recent study showed that natural killer cell activation distinguishes TB-IRIS from chronic HIV and HIV-TB co-infection [12]. An increased host genetic susceptibility to exuberant immune recovery [13] or a functional defect of the regulatory T-cells [14] are other potential mechanisms which may contribute to the development of IRIS in certain individuals.

Different types of IRIS

Tuberculosis

The frequency of paradoxical TB-IRIS ranges from 8 to 43%, and usually occurs within the first few weeks up to 3 months after ART initiation [2]. Risk factors include low CD4 counts, disseminated and extrapulmonary TB, a shorter period between anti-TB and ART initiation, and an exuberant immunological and virological response to ART [2]. Common presentations of paradoxical IRIS include fever, new or enlarging lymph nodes, cold abscess or other focal tissue involvement, new or worsening radiological features of TB, central nervous system (CNS) TB, serositis, constitutional or respiratory symptoms, abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy [2]. The reported median duration of symptoms is 2 months (range: a few days to more than a year) [2]. TB-IRIS produces substantial morbidity, frequently requiring hospitalisation and the needle aspiration of abscesses [15].

Paradoxical neurologic TB-IRIS is a potentially life-threatening condition and accounted for 12% of TB-IRIS in a prospective observational study in South Africa [16]. Of 23 patients with paradoxical neurologic TB-IRIS, eight presented with meningitis, seven with tuberculoma, five with both meningitis and tuberculoma, and three with radiculomyelopathy. Twenty (87%) required hospitalisation and 21 received corticosteroids. Six months after the initial assessment for neurologic deterioration, 70% were still alive, 13% died and 17% were lost to follow-up [16].

Despite the increased risk of developing IRIS with the early initiation of ART, particularly in patients with CD4 cell counts <50 cells/μL, ART should be started within 2 weeks after starting TB treatment in order to reduce mortality [17–19].

Although glucocorticoids have been proposed as the therapeutic agent for paradoxical TB-IRIS [20], limited evidence exists for this recommendation [21]. In a randomised, double-blind, placebo-controlled trial, prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) significantly reduced the duration of hospitalisation and outpatient therapeutic procedures, and led to more rapid improvements in the symptoms and quality of life among patients with TB-IRIS [22]. Infections occurred more often in the prednisone than in the placebo arm, but there was no difference in the incidence of severe infections [22].

Non-tuberculous mycobacteria

Non-tuberculous mycobacteria (NTM) infection, including *Mycobacterium avium* complex (the most common), *M. leprae*, *M. genavense*, *M. kansasii*, *M. scrofulaceum* and Bacillus Calmette-Guerin (BCG), can be a cause of IRIS [23–25]. The incidence of NTM-associated IRIS was 3.5% in a study in the United States [23]. The median interval from the initiation of ART to the onset of symptoms of

NTM-IRIS was 3 weeks [23]. In a review of 44 NTM-IRIS cases, 69% presented with lymphadenopathy and 19% with pulmonary disease [25]. Involvement of the musculoskeletal system (septic arthritis, osteomyelitis, psoas abscesses and pyomyositis), skin and hepatosplenomegaly has also been described [25]. Intra-abdominal NTM-IRIS accounts for a higher proportion of hospitalisations than NTM-IRIS involving other sites [23].

Cryptococcal infection

The incidence of paradoxical cryptococcal-IRIS is estimated to be between 8 and 49% [8]. The reported time of onset of paradoxical cryptococcal-IRIS after the initiation of ART varies from 1 to 10 months (range 4 days to 3 years). Reported risk factors for paradoxical cryptococcal-IRIS include early ART initiation (<1–2 months after antifungal therapy), substantial increase of CD4 cell count in the first 6 months of ART and high fungal load at the diagnosis of cryptococcosis [8]. On the other hand, the incidence of ART-associated cryptococcosis ranges from 0.2 to 1.6%, with a median time of diagnosis of 4 weeks (interquartile range [IQR] 2–10 weeks) after the start of ART. The clinical spectrum of paradoxical cryptococcal-IRIS and ART-associated cryptococcosis are similar, with meningitis, lymphadenopathy, intracranial space-occupying lesion(s), multifocal disease, cutaneous or soft-tissue lesions and pneumonitis being the most common manifestations [8]. The reported mortality from paradoxical cryptococcal-IRIS and ART-associated cryptococcosis ranged from 27 to 83% in Africa and from 0 to 20% in North America, Europe and southeast Asia [8]. Therapies that have been used in the management of cryptococcal-IRIS include corticosteroids, non-steroidal anti-inflammatory drugs and thalidomide, but for none of these treatments is there strong evidence of efficacy [8].

To fulfill the proposed INSHI case definition for paradoxical cryptococcal-IRIS, the symptoms should develop within 12 months after ART initiation. A negative cryptococcal culture is not an absolute requirement for the diagnosis of IRIS, given the variable timing of cerebrospinal fluid (CSF) culture sterility in patients treated with amphotericin B or high-dose fluconazole. Nevertheless, a positive fungal culture after 3 months of antifungal therapy is considered as therapeutic failure, excluding the diagnosis of IRIS [8]. Additionally, declining CSF cryptococcal antigen titres are not considered to be helpful, since, at the time of IRIS, 25% of 85 patients had negative cultures accompanied by a less than 4-fold decrease in CSF cryptococcal antigen titre [26].

Viral infections

Herpes, warts and *Molluscum contagiosum*

In an HIV clinic in London, genital herpes and varicella zoster virus infections accounted for more than 50% of the IRIS events, and genital warts and *Molluscum contagiosum* for, respectively, 23% and 9% of the IRIS events [27]. IRIS-related CNS complications of herpes simplex virus and varicella zoster virus are rare, but they may cause permanent neurological disability or death [1, 28, 29].

Appropriate antiviral therapy is the mainstay of the treatment. Corticosteroids should not be used routinely, given the lack of evidence of their effectiveness. Their use should only be considered when there is a risk of permanent neurological damage secondary to IRIS.

Cytomegalovirus

In the first 3 months following ART, CMV retinitis may be an IRIS manifestation occurring at an incidence of 2.7–3.6/100 person-years [30]. CMV immune recovery uveitis usually occurs later in the course of ART treatment and, presumably, results from specific immune restoration against residual CMV antigens located in the eye. Most uveitis patients have a previous history of CMV retinitis and the larger the proportion of retinal involvement, the higher the risk of developing IRIS uveitis [31]. Topical or systemic corticosteroid therapy is usually effective [31].

Progressive multifocal leukoencephalopathy

ART-associated immune reconstitution is thought to contribute substantially to the number of new cases of progressive multifocal leukoencephalopathy (PML). Four observational cohort studies from industrialised countries report incidences of PML-IRIS varying between 23 and 37% [32–35].

PML carries a high morbidity and mortality rate [36, 37]. In a recent study, no differences in survival were observed between patients with PML with or without IRIS [38]. Predictors of a better prognosis include a higher CD4 count at PML diagnosis, detectable cytotoxic T-lymphocytes in blood, contrast enhancement of PML lesions and IRIS [37, 39]. The diagnosis of PML-IRIS is usually based on characteristic clinical (focal weakness, cognitive dysfunction, visual disturbance and impaired coordination) and neuro-radiological findings (contrast-enhancing lesions on neuro-imaging [34]) in the context of ART after the exclusion of other opportunistic infections or malignancies of the CNS. However, PML-IRIS does not always seem to

generate sufficient inflammation to be visible on neuroimaging [40]. Brain biopsies show marked perivascular and intraparenchymal infiltration by macrophages and CD8+ T-lymphocytes [41–43]. The determination of JC virus DNA by polymerase chain reaction in CSF is often positive.

There is no specific therapy for JC virus infection, but prognosis is improved by ART [41, 44, 45]. Conflicting data exist on the role of corticosteroids in PML-IRIS [46]. Some authors suggest a beneficial effect [36, 47], while others caution against their use based on the finding that an inflammatory response in the brain is associated with a favourable outcome [40–42].

Hepatitis B and C

The diagnosis of viral hepatitis-associated IRIS is a challenge, since many other common conditions can cause hepatotoxicity after ART initiation, mimicking a hepatic flare associated with viral hepatitis-associated IRIS. Viral hepatitis- associated IRIS is usually defined as an increase in the alanine transaminase (ALT) level>5 times the upper limit of normal and/or >200 IU/L higher than at baseline in a patient on an effective ART regimen, without another explanation for this increase.

In a study of 36 patients with a hepatitis B virus (HBV)-HIV co-infection, after the commencement of ART, 22.2% of the patients developed HBV-IRIS [48]. Patients who developed HBV-IRIS had significantly higher levels of HBV DNA and ALT at baseline than a control group [48].

In a prospective study from Indonesia, 18% of patients with positive anti-hepatitis C virus (HCV) antibodies prior to ART developed IRIS related to HCV (incidence 9.2 per 1,000 person-weeks) [49]. In this study, 78% of the patients experienced mild symptoms (nausea and vomiting), and the ALT elevations resolved without any change in therapy. On the other hand, in a retrospective study from Australia, only 2% of the patients who started ART without previous clinical signs of HCV infection developed symptomatic HCV-IRIS [50]. Splenomegaly, jaundice and rapidly evolving cirrhosis were also reported as manifestations of HCV-IRIS [50, 51].

Neuro-IRIS caused by HIV?

Certain patients may develop neurological manifestations caused by a meningo-encephalitis with diffuse white-matter abnormalities after the start of ART. In some of these patients with neuro-IRIS, no evidence of a co-infection is found [52]. In such cases, the underlying antigenic stimulus may be components of HIV itself or self-antigens. Another possibility is that the leakage of HIV or other viruses (e.g. Epstein-Barr virus [EBV]) across the blood–brain barrier may serve as an antigenic provocateur. In the CSF, a lymphocytic pleocytosis can be found and the immunohistochemical analysis of a brain biopsy can reveal an inflammatory-cell infiltrate composed predominantly of CD3 and CD8 T-cells [53]. Recently, a case of neuro-IRIS, 2 years after starting ART, potentially caused by HIV, was described. The neurological symptoms of this patient disappeared after corticosteroid treatment [3].

Kaposi's sarcoma

In a study from Mozambique, 11.6% HIV-1 and Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) co-infected patients experienced KS-IRIS at a median time of 13.8 weeks after ART initiation [54]. Clinical pretreatment KS, detectable plasma KSHV DNA, a hematocrit <30% and a high plasma HIV-1 RNA viral load were risk factors for IRIS [54]. In a study in the United Kingdom, the incidence of KS-IRIS was 6.6% in patients with KS already present pre-ART [55]. The rapid progression of cutaneous or mucocutaneous lesions are the most common manifestations, while pulmonary and lymphatic involvements have also been reported [56]. ART can be continued safely in most patients, but systemic chemotherapy may be required in patients with severe forms of KS [56]. To prevent the development of KS-IRIS, it is important that patients with severe forms of KS should receive chemotherapy before the start of ART.

Parasitic infections

Toxoplasma

Toxoplasmosis is one of the most frequent causes of focal intracerebral lesions complicating acquired immunodeficiency syndrome (AIDS). The prevalences of toxoplasma-IRIS range from 1.5 to 9.5% [57–59]. We found 17 cases of cerebral toxoplasma-IRIS reported in the literature [60–65]. Clinical manifestations include confusion, headache, hemiparesis, generalised seizures and/or imbalance. Symptoms appeared after a median of 105 days after the initiation of ART [61, 62, 65]. The baseline CD4 count was mostly below 200 cells/μL [60, 62, 64, 65], but one patient had a baseline CD4 count of 456 cells/μL [61]. Neuro-radiological imaging generally shows typical ring-enhanced lesions [63, 65].

Schistosomiasis

Three cases of *Schistosoma mansoni*-related IRIS were diagnosed in high-income countries among immigrants from countries where *Schistosoma* infection is endemic [66–68]. One patient presented with eosinophilia and

hepatosplenomegaly [66], the second with vomiting, diarrhoea and abdominal pain [67], and the third with schistosomal colonic polyposis [68]. All three cases were unmasking IRIS cases. Preliminary reports of a study in Kenya identified nine cases of schistosomiasis-IRIS in 51 patients initiating ART [69].

Strongyloides stercoralis

Four possible cases of unmasking IRIS [70–73] and one case of paradoxical IRIS [74] associated with *Strongyloides stercoralis* have been described. The median baseline CD4 count was 48 cells/μL. Symptoms developed after a median of 6 weeks after the initiation of ART and consisted of cough, pneumonitis, gastrointestinal complaints, eosinophilia, fever and hepatitis.

Leishmaniasis

We found 25 case reports of leishmaniasis-related IRIS in the literature [75–95], Of these, seven patients showed more than one episode of reactivation after the start of ART, so a total of 33 episodes were noted. Thirteen were unmasking, 15 were paradoxical cases of IRIS and the remaining cases were unknown. The median baseline CD4 count was 60 cells/μL. Symptoms of IRIS started after a median of 4 months after ART initiation and consisted of fever, hepatosplenomegaly, anaemia, leukopaenia, thrombocytopaenia, gastrointestinal complaints, renal insufficiency and skin lesions (papular and nodular lesions, maculopapular rashes and mucosal lesions). IRIS presented as post-kala-azar dermal leishmaniasis (PKDL) in 16 (53.3%) patients, visceral leishmaniasis (VL) in 9 (30%), uveitis in 2 (6.7%), and both PKDL and VL in 2 patients and PKDL and uveitis in 1 (3.4%) case.

Other parasitic IRIS cases

A case of IRIS related to *Cryptosporidium* spp. infection and another related to a microsporidium infection have been reported [96, 97].

Conclusions

Despite the improved access to antiretroviral therapy (ART), which considerably improved the life expectancy of persons with human immunodeficiency virus (HIV), patients continue to present late, when their immunity has dropped to a low level [98]. Those patients are at risk of the immune reconstitution inflammatory syndrome (IRIS). IRIS is complicating patient care and can be a cause of mortality. Patients may lose confidence in the health care providers because their health is supposed to improve during ART and not become more ill. They may stop ART and treatment for their opportunistic infection. In order to diagnose IRIS, one has to first exclude other causes that could explain the worsening condition of the patients. Certainly in developing countries, this may be difficult because diagnostic facilities to exclude these conditions may not be available. Physicians may start corticosteroid therapy in patients suspected of IRIS but who do not have IRIS. This may lead to disseminated infections and death.

The general approach to the treatment of IRIS is to continue ART and treat the co-infection. Anti-inflammatory therapy should not be given routinely but, instead, reserved for those patients with severe inflammation, particularly when the condition is life-threatening, e.g. in the case of a central nervous system (CNS) infection with cerebral oedema. Given that a low CD4+ T-cell count is a major risk factor for the development of IRIS, commencing ART at a CD4+ T-cell count >350/μL will prevent most cases.

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