Cryptococcal Immune Reconstitution Inflammatory Syndrome

Subjects: Pathology

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Immune reconstitution inflammatory syndrome (IRIS) presents as an exaggerated immune reaction that occurs during dysregulated immune restoration in immunocompromised patients in late-stage human immunodeficiency virus (HIV) infection who have commenced antiretroviral treatments (ART). Virtually any opportunistic pathogen can provoke this type of immune restoration disorder.

immune reconstitution inflammatory syndrome (IRIS) AIDS/HIV antiretroviral therapy (ART) cryptococcal meningitis (CM) blood biomarkers cerebrospinal fluid biomarkers

1. Introduction

Cryptococcus species are the most common cause of meningitis in adults and one of the leading causes of human immunodeficiency virus (HIV)-related mortality in the world, with a global incidence estimated at 223,100 cases per year [1][2]. In countries with limited resources, cryptococcosis drives up to 40% of all hospitalizations and deaths associated with the advanced stage of HIV infection [3][4][5]. Immune reconstitution inflammatory syndrome associated with cryptococcosis (C-IRIS) is a common complication that manifests after the initiation of antiretroviral therapy (ART) [6][7]. Cryptococcal IRIS presents as an exaggerated and deregulated proinflammatory immune reaction, which accompanies the reduction in peripheral blood HIV viral load and the initiation of CD4+ T cell recovery [7]. Approximately 25% of HIV and *Cryptococcus* co-infected patients develop cryptococcal meningitis IRIS (CM-IRIS) within the first four months of ART treatment, with an average mortality rate of around 20 +/− 10% [8].

There are two recognized forms of CM-IRIS. The first form is “unmasking” IRIS, in which the individual manifests an inflammatory response to *Cryptococcus spp.*, revealing previously undiagnosed cryptococcal meningitis (CM) in ART-naïve individuals after starting ART [7][9]. Unmasking CM-IRIS may include neurological symptoms driven by high intracranial pressure and inflammation, such as severe headaches, vomiting, visual impairment (diplopia, photophobia, blindness), hearing loss, seizures, ataxia, or aphasia [10][11][12]. Altered mental status, including personality and behavioral changes, confusion, hallucinations, and in rare cases, lethargy, are attributable to unmasking CM-IRIS. Unmasking IRIS is usually diagnosed within 2 to 6 weeks on antiretroviral treatment and it is the deadliest [13]. Thus, the diagnosis of cryptococcal infection is essential for the prevention of unmasking CM-IRIS. The second form is “paradoxical” IRIS, which occurs in the settings of induction antifungal therapy [6][14]. Paradoxical CM-IRIS became the most common due to significant improvements in the diagnosis of cryptococcal

meningitis and the introduction of antifungal therapy regimens prior to ART commencement [6][15]. The paradoxical form also presents itself as neuro-cryptococcosis, with clinical symptoms of worsening neurological function impairments and altered mental status due to raised intracranial/cerebrospinal fluid (CSF) pressure. Paradoxical CM-IRIS can be clinically assessed according to Glasgow Coma Scores (GCS > 15) and via MRI imaging findings (e.g., multifocal or diffuse leptomeningeal and cortical enhancements) [14][16][17][18]. Paradoxical C-IRIS manifests, on average, 1 to 6 months after the initiation of ART, and it occurs in the background of initial clinical and microbiological response to antifungal treatment, as well as virologic response to ART [2][14][19]. As described below, periodic examination of cerebrospinal fluid was found to be helpful to diagnose and predict paradoxical CM-IRIS [20].

Pulmonary C-IRIS has been described primarily in *Cryptococcus neoformans* infection. Clinical manifestations include cough, dyspnea due to pneumonitis, pulmonary infiltrates, lymphadenopathy, cavitation, and nodular lesions [9][21][22]. Several components of the immune system such as T cells and macrophages, pro-inflammatory cytokines and chemokines are thought to be involved in the pathology of pulmonary C-IRIS, although they have not been systematically studied (reviewed in [23]).

2. Conventional Risk Factors for CM-IRIS

The conventional risk factors of CM-IRIS can be divided into three categories.

2.1. Host-Related Risk Factors

Because the variety of opportunistic pathogens has been linked to ART-associated IRIS in people with acquired immunodeficiency syndrome (AIDS), host-related risk factors are considered most important and universal for several types of IRIS [24]. Improvements in immune status in patients who have been severely immunocompromised are often accompanied by disbalanced immune reconstitution, which represents a host risk factor for the development of IRIS. Patients, as such, have very low pre-ART CD4+ T cell count in the blood (<100 CD4+ cells/uL) [25][26] and high HIV viral load (>100,000 copies/mL of blood) [27]. They include low baseline antibody responses to *Cryptococcus spp.*, e.g., decreased levels of total plasma IgM and specific antifungal IgM (GXM-IgM or β-glucan-binding IgM) [28], and a lack of pro-inflammatory cytokines in the serum, or CSF, as described below. Genetic factors, such as single nucleotide polymorphism Interleukin 7 receptor subunit alpha (IL7RA), may affect predisposition in the development of IRIS [29]. Allelic polymorphisms (e.g., in CYP2C19 gene) may be considered as patient-specific risk factors affecting fungicidal drug activities, toxicity, and the level of inflammation (e.g., C-reactive protein or albumin levels) [30]. More recently, transcriptomic profiles have been assessed, and several molecular pathways were proposed (as potential baseline biomarkers), as described below [31]. Among readily available baseline biomarkers, low hemoglobin concentrations (<8.5 g/dL), high C-reactive protein levels (CRP > 32 mg/L) or D-dimers (>3.89 ug/mL) are predictive of IRIS events [8][15].

2.2. Pathogen-Related Risk Factors

The genomic differences in clinical isolates may underlay differential drug susceptibility and virulence of *Cryptococcal spps*., which play important roles in the severity of CM and CM-IRIS [32]. Genetic make-up allowed some *Cryptococcal spps*. advantaged metabolic fitness, as was tested in pre-clinical models [33][34][35]. Mutated species of HIV may also play roles in the pre-treatment drug resistance to non-nucleoside reverse transcriptase inhibitors ART, and in alterations of immune responses after ART initiation [36].

In recent years, there has been an international collaborative effort focused on the development of point-of-care assays in resource-limited laboratory settings [37][38]. The lateral flow assay (LFA, IMMY® diagnostics, Norman, OK, USA) utilizes gold-conjugated monoclonal antibodies that target capsular polysaccharide glucuronoxylomannan (GXM), a primary cryptococcal antigen of four serotypes [39]. LFA is fast and able to quantify cryptococcal antigen (CrAg) titers with high sensitivity and specificity in CSF: 100% and 99.8%, respectively (reviewed in [40]). Cryptococcal antigenemia (CrAg+) in serum, CSF or other biofluids is often detected in asymptomatic CM patients who subsequently develop CM-IRIS [41][42][43][44]. Mortality also remains higher in CrAg+ immunocompromised patients after initiation of ART, and the levels of CD4+ T cells are inversely correlated with CrAg titers [45][46]. The FDA-approved BioFire FilmArray® meningitis/encephalitis nested multiplex PCR panel (bioMérieux, Salt Lake City, UT, USA) has recently been introduced into routine clinical practice, and it can detect and differentiate DNA from *C. neoformans* and *C. gattii* (among other pathogens) [47].

With the development of highly sensitive and specific molecular tests, great advances have been made in the diagnostic procedures of CM caused by various Cryptococcal species. Isothermal molecular techniques, such as LAMP (Loop-mediated isothermal AMPlification), have also contributed to improving the diagnosis of fungal diseases. The LAMP technique is based on the principle of isothermal loop amplification to identify the species of *Cryptococci* from the CSF culture isolates targeting the internal transcribed spacer (ITS) region and CAP59 gene. The LAMP assay has high specificity for molecular genotypes VNI, VNII, and VNIII of *Cryptococcus neoformans*, and is able to differentiate from *C. gattii* and other fungal species [48]. LAMP does not require expensive laboratory instrumentation to perform, thus in the future it can be introduced as a point-of-care assay.

Culture remains a gold standard to assess live pathogens in the CSF or blood, by measuring colony-forming units (CFU/mL) growth on Sabouraud dextrose agar for 48 h at 30 °C. An important prognostic parameter, such as early fungicidal activity (EFA), can be calculated from recurrent cultures during induction regimens (described below). Microbiological clearance is measured as $\log_{10}$ clearance of *Cryptococcus* yeasts per mL of CSF and serves as an important predictor of increased mortality, including that from C-IRIS [49]. Cultured isolates can subsequently be serotyped by real-time PCR assay, and mating type can be determined by amplified fragment length polymorphism (AFLP) or PCR-restriction fragment length polymorphism (PCR-RFLP) [34][50]. Molecular typing revealed that genotypes, drug susceptibility, and the virulence of *Cryptococcus* species varied between different continents and in different countries [51]. However, recent studies found no correlation between antifungal drug susceptibility and hazards of death for therapeutic outcomes in the cohort of severely immunosuppressed AIDS patients [52].

2.3. Treatment-Related Risk Factors

Inadequacy of high-dose antifungal drug monotherapy or combination therapy is the number one treatment-related factor for IRIS, as mortality from CM is the highest during the first 6 months under routine protocols [53][54]. A combination of various antifungal regimens has been tested and compared in the procurement of the best antifungal activity in the shortest period of time [55][56]. However, a shorter duration between induction antifungal treatment and the initiation of ART may predispose patients to fatal C-IRIS events. The proposed explanation is an insignificant time for the achievement of microbiological clearance [54][57].

A combination of highly active antiretroviral drugs seems to have immunomodulatory effects, yet in some cases increases IRIS incidence, depending upon patient-specific factors [58]. The rapid decrease in HIV viral load on ART (>2.5 log reduction in IRIS patients, over 4 weeks, when compared to pre-ART viral load) has also been identified as a risk factor for activation of the host immune system and IRIS [27][59][60]. On the other hand, the interruption of ART or development of ART resistance slows down the immune reconstitution and prolongs chronic inflammation [61][62]. After ART initiation, confirmation of the virologic response is highly recommended for the diagnosis of treatment failure or suboptimum responses to combination ART, but it is not essential for the prediction of IRIS [63][64].

Thus, rapid cellular immune activation that drives the symptoms of CM-IRIS is predicated by a combination of several factors, such as the hosts' immunological predisposition, the microbial antigen burden, and the effectiveness of the drugs (ART or antifungals).

3. Immunopathogenesis of C-IRIS

Human immunodeficiency virus infects and persists in CD4+ T cells, astrocytes, microglial cells, and less frequently, in cells of monocyte-macrophage lineage [65][66]. During the first few weeks on ART, the rate of HIV viral load decreases and T cell population stabilizes; however, the recovery initiates very slowly in severely immunodeficient individuals. The initiation of ART at the advanced stage of HIV infection (at CD4+ T cells ≤ 200/mm^3) is associated with long-term immune and metabolic abnormalities (up to 3 years after ART initiation) [67]. In fact, the thymic output of naïve CD4+ T cells (detected as T cell receptor excision circles (TRECs)) exhibits an augmenting trend only after 12 months on ART in adults and young children [68][69]. Pre- and post-ART, CD4+, and CD8+ T cells express immune checkpoint molecules (e.g., PD-1, TIGIT, and LAG-3), which are associated with long-term HIV persistence and immune exhaustion [70]. During IRIS episodes, higher frequencies of PD-1+/CD4+ T cells expressing LAG-3, CTLA-4, and ICOS have also been detected when compared with patients without IRIS [71]. HIV-AIDS patients, who subsequently die from CM-IRIS or CM after ART initiation, also exhibit upregulation of immune checkpoint gene expression (PD-1, PDL-1) in peripheral blood at the time of ART (Vlasova-St. Louis, unpublished). The persistence of expression of immune checkpoint molecules and T cell immune exhaustion correlates with the increased size of the HIV reservoir, which seems to play an important role in the subsequent ART-driven activation of cytotoxic CD8+ T cells and antigen-presenting cells [72][73]. This may lead to unproductive and paradoxical immune reactions to a reservoir of antigens, secretion of pro-inflammatory mediators by activated monocytes and macrophages, and tissue damage [74]. Thus, the transition from the state of immune exhaustion

and poor macrophage function to ART-related immune reconstitution is often accompanied by exaggerated innate inflammatory responses which lead to IRIS.

4. Treatment Advances for the Management of Cryptococcal Infection and C-IRIS

With respect to therapies, there are still no effective treatments for C-IRIS; however, targeting the risk factors described in 2.2 may decrease IRIS incidence and severity. The CM treatment regimens are composed of three pharmaceuticals: amphotericin B deoxycholate (AmB) or liposomal AmB (L-Amb), flucytosine (5-FC), and fluconazole (FLU) (Table 1). The treatment of CM is divided into three phases: induction, consolidation, and maintenance (reviewed in [75]).

Table 1. Treatment advances for the management of cryptococcal infection with antifungal drugs.

Drug	Findings	Reference
Amphotericin B deoxycholate (AmB), 1 mg/Kg/day	Hepatic and renal toxicity Side effects: Anemia Electrolytic abnormalities Reactions at the site of infusion	Lawrence et al., 2018 [76] Molloy et al., 2018 [77] Molefi et al., 2015 [78]
Liposomal AmB (L-AmB) 10 mg/Kg	Less toxic Single dose administration Longer half-life More effectively penetrates the brain tissues	Lawrence et al., 2018 [76] Molloy et al., 2018 [77] Molefi et al., 2015 [78]
Encochleated amphotericin B deoxycholate (cAMB) 1–2 g per day	In test-EnACT Trial	Skipper et al., 2020 [79]
Flucytosine (5-FC)	Provides most effective fungicidal activity when combined with AmB	Concha-Velasco et al., 2017 [80]

Drug	Findings	Reference
50–150 mg/kg/day		
Voriconazole (VCZ) 400 mg/day	Good bioavailability Higher cost No statistically significant differences between VCZ and AMB/FLU or AmB/5-FC	Loyse et al., 2012 [81] Li et al., 2016 [82] Zeng et al., 2020 [83]
Posaconazole Isavuconazole Itraconazole	Used as a second-line agent in combination with AmB Exhibit drug–drug interactions and toxicity	Wong et al., 2020 [84] Jørgensen et al., 2019 [85] Houšť et al., 2020 [86]
VT-1129	Highly selective for fungal CYP51 Minimal effect on human cytochrome P450	Lockhart et al., 2016 [87] Nielsen et al., 2017 [88]
Fluconazole (FLU) 200 mg/day	Maintenance phase of CM treatment	Quan et al., 2019 [89] Bongomin et al., 2018 [90]

Abbreviation: CM—cryptococcal meningitis.

The induction phase aims to drastically decrease the fungal burden in the patient's cerebrospinal fluid in the first 2 weeks and is fundamental for survival. AmB has high toxicity at standard doses of 1 mg/kg/day, such as hepatic and renal toxicity, anemia, electrolytic abnormalities, or reactions at the site of infusion. For this reason, a recent formulation of liposomal amphotericin B (L-AMB) has been recommended as it is less toxic at a single dose (10 mg/kg), has a longer half-life, and more effectively penetrates the brain tissues [76][77][78]. Presently, the combination AmB/5-FC provides the most effective fungicidal activity and cryptococcal clearance [80]. A novel formulation of oral AmB is currently being tested for safety and tolerability in the EnACT Trial [79].

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Voriconazole (VCZ) is an antifungal agent that is used to treat invasive fungal infections, such as cryptococcosis, aspergillosis, and candidiasis. A study conducted in South Africa assessed its efficacy in treating CM and showed no statistically significant difference between the use of AmB/FLU or AmB/voriconazole and the standard AmB/5-FC therapy [81][82]. VCZ has good bioavailability, but owing to a higher cost, scarcity of studies on CNS penetration, and altered pharmacokinetics in the context of inflammation, its use is limited [83]. Although other triazoles such as itraconazole, posaconazole, and prodrug isavuconazole [84][85] exhibit anticryptococcal activity, they are only used as a second-line agent or in combination with AmB due to drug–drug interactions and toxicity (reviewed in [86]).

In the consolidation phase (2–6 weeks of induction therapy), doses of antifungal agents are decreased, and antiretroviral therapy is initiated. The timing of ART initiation in the consolidation phase should be considered carefully [91]. The introduction of ART is recommended 4–6 weeks after starting induction antifungal therapy to improve survival rates and achieve sustained clinical responses [92]. A pragmatic approach to the management of patients with HIV-associated cryptococcal meningitis has been outlined in a recent study [93]. Recently, a new tetrazole compound, VT-1129 (Viamet Pharmaceuticals Inc.), has been shown to exhibit potent in vitro activity against *Cryptococcus spp*. [87]. VT-1129 is highly selective for fungal CYP51, has minimal effect on human cytochrome P450 enzyme metabolism, and may potentially be used as a preemptive or consolidation therapy for fluconazole-resistant cryptococcal meningitis [88].

The maintenance phase is introduced to maintain the sterility of CSF culture and to prevent a relapse of cryptococcal disease. The fluconazole maintenance therapy (200 mg/day) is extremely important; however, this phase is the most vulnerable to non-compliance and loss to follow-up [89][90].

There are three main approaches to combat C-IRIS: supportive care aiming to reduce host-related risk factors), symptomatic treatment of high intracranial pressure, in cases of CM-IRIS, and anti-inflammatory, or immunomodulatory approaches to diminish inflammation.

The symptoms of paradoxical CM-IRIS are accompanied by abnormal radiographic imaging findings and high intracranial pressure (>250 mm H_2O) [14]. Thus, as a symptomatic treatment, therapeutic lumbar punctures and, in some cases, shunting are recommended for those suspected of CM-IRIS [94][95]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the cases of mild and self-contained forms of CM-IRIS. In cases of severe symptoms of CM-IRIS, the administration of corticosteroids (particularly, dexamethasone) has been found to be beneficial to decrease inflammation, although it has also been shown to be associated with higher mortality [96]. A [97][98]. In cases of pulmonary cryptococcal IRIS, corticosteroid treatment may be considered in the event of the development of respiratory distress, but the antifungal regimens should be continued [87][88]. The immunosuppressive drug hydroxychloroquine reduces lipopolysaccharide/TLR-mediated immune signaling, which may be important for CM-IRIS prevention, as early CM-IRIS is solely driven by innate immune activation pathways, especially in immunological non-responders (patients with CD4+ T cell increase of <5% in the last 12 months on ART) [99] (Table 4).

Table 4. Treatment advances for the management of CM-IRIS with anti-inflammatory agents and biologics.

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Drug/Treatment	Findings	Reference
Therapeutic lumbar punctures/shunting	Recommended for high intracranial pressure	Govender et al., 2019 [94] Cherian et al., 2016 [95]
Corticosteroids (dexamethasone, prednisone, prednisolone) 0.3–1 mg/kg/day	Decreases inflammation, but associated with higher mortality Reduces TLR-mediated immune activation	Beardsley et al., 2019 [96] Day et al., 2014 [97] Beardsley et al., 2016 [98]
Hydroxychloroquine 400 mg/day	Neurological improvement in severe C-IRIS cases	Piconi et al., 2011 [99]
Thalidomide/Adalimumab 100 mg per day	Bind to TNFα and block its anti-inflammatory activity Expedites fungal clearance	Brunel et al., 2012 [100] Gaube et al., 2016 [101]
Recombinant IFNγ (Immukin, Boehringer Ingelheim) 100–200 µg s.c.	Increases Th1 cell responses Depolarizes macrophages No evident benefit to patient survival	Jarvis et al., 2012 [102] Gamaletsou et al., 2012 [103]

Other immunomodulatory agents (such as thalidomide or adalimumab) have been tested in severe cases of CM-IRIS. Several reports documented neurological improvement after the use of thalidomide and adalimumab—human monoclonal antibodies that bind to TNFα and block its anti-inflammatory activity [100][101]. Another biologic, a recombinant IFNγ, has been shown to expedite CSF fungal clearance by increasing Th1 cell responses and depolarizing macrophages, although it has failed to exhibit evident benefits to patient survival [102][103]. In all cases of C-IRIS, ART should be continued unless there is a risk of fatal outcomes [104][105] (Table 4).

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