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HIV and Immune Reconstitution Inflammatory Syndrome (HIV-IRIS)

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Abstract

The development of antiretroviral therapy (ART) has markedly improved the outlook for patients living with human immunodeficiency virus (PLHIV). However, in a subset of patients, dysregulated immune response after initiation of ART leads to the phenomenon of immune reconstitution inflammatory syndrome (IRIS). A multitude of names have been applied to these situations including immune restoration disease and immune reconstitution inflammatory syndrome (IRIS). HIV- associated IRIS has emerged as an important early complication of ART initiation, associated with considerable morbidity and mortality, particularly in patients who commence ART with advanced immunosuppression. Numerous infective and no infective conditions are associated with IRIS in HIV infection. The commonest forms are associated with mycobacterial infections, fungi and herpes viruses. Timing of ART initiation is critical to reduce IRIS-associated mor¬bidity. Clinicians need to remain vigilant when initiating ART and individualize therapy according to known treatment options for the specific infectious agent.

Keywords: Human immunodeficiency virus; Immune reconstitution inflammatory syndrome; Tuberculosis

List of abbreviations: ART: Anti-retroviral Therapy; BCG: Bacillus Calmette–Guérin; CMV: Cytomegalovirus; CNS: Central Nervous System; EBV: Epstein–Barr Virus; HSV: Herpes Simplex Virus; HHV-8, Human Herpes Virus-8 (Kaposi's sarcoma virus); HPV: Human Papilloma Virus; IRIS: Immune Reconstitution Inflammatory Syndrome; JC: John Cunningham; NTM: Nontuberculous Mycobacteria; OI: Opportunistic Infection; PCP: *Pneumocystis Jirovecii* Pneumonia; PML: Progressive Multifocal Leukoencephalopathy; SLE: Systemic Lupus Erythematosus; TBM: Tuberculoses Meningitis; VZV: Varicella zoster virus

Introduction

Combination ART substantially reduces the occurrence of opportunistic events and mortality in PLHIV. The beneficial effects of ART result from gradual restoration of pathogen-specific immune responses, mediated by suppressed HIV replication and increased CD4 cell count [1,2]. However, subgroups of patients experience a clinical deterioration as a consequence of rapid and dysregulated restoration of antigen specific immune responses during the treatment [3]. The immune pathological inflammatory response is reminiscent of similar clinical worsening seen in occasional non HIV patients being treated for tuberculosis or leprosy. Similarly the clinical worsening in some patients following bone marrow transplantation also has the immuno inflammatory basis [4]. Among HIV infected patients, IRIS was first noted following the introduction of zidovudine monotherapy in the early 1990s, when French *et al.* reported a case series of unusually localized Mycobacterium avium-intracellulare (MAI) infections presenting with fevers and lymphadenitis without mycobacteraemia, which developed soon after commencement of zidovudine monotherapy [3,5,6]. The introduction of ART was quickly followed by numerous reports of patients in whom recovery of immune responses led to clinical worsening. Initially, the induction of immunity engendered by ART was most clearly demonstrated in the case of hepatitis B virus infection where serial antibody measurements could be correlated with the clinical course [7]. A variety of opportunistic pathogens including viruses (human herpesvirus-8 and cytomegalovirus), fungi (Cryptococcus, Pneumocystis and Histoplasma) and bacteria (Mycobacterium) are associated with the development of IRIS after initiation of ART [1,2,8]. In this review, we describe the spectrum of HIV-associated IRIS.

Definitions

IRIS is defined as a paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating ART in PLHIV resulting from restored immunity to specific infectious or non-infectious antigens [9,10]. There are two forms of IRIS:

paradoxical or unmasking. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an ART-associated inflammatory manifestation of a subclinical infection with a hastened presentation. In this latter form signs and symptoms not clinically apparent before, appear during ART [6,11]. Because clinical deterioration occurs during immune recovery, this phenomenon has been described as immune restoration disease (IRD), immune reconstitution syndrome (IRS), and paradoxical reactions. Given the role of the host inflammatory response in this syndrome, the term (IRIS) has been proposed and has become the most widely used and accepted term to describe the clinical entity [1,9].

Diagnostic criteria for IRIS

There is no single diagnostic test currently available for IRIS. Therefore, information regarding the opportunistic infections (OI) involved, diagnosis, treatment and response to treatment of OI before the start of ART is crucial to the diagnosis of "paradoxical" IRIS. Diagnosis is further complicated in patients with "unmasking" IRIS, as it is difficult to prove both the previous existence of a hidden OI and that the observed increase in inflammation is due to immune recovery. Thus, French *et al.,* have laid down criteria so as to aid the diagnosis (Table 1) [12]. They recommended two major and three minor criteria for the diagnosis of IRIS. They defined these two major criteria as identification of atypical presentation of OI and decrease in HIV RNA expression by >1 log after ART. The three minor criteria are defined as an increase in CD4+ cell count, increase in immunological response to OI and spontaneous recovery of clinical symptoms [13]. However, the confirmatory diagnosis is often complicated due to factors such as drug resistance, drug interactions, treatment failure of the OI and other possible OI [8].

General IRIS case definition proposed by French, et al. (2004)
Diagnosis requires two major criteria (A+B) or major criterion (A) plus two minor criteria to be fulfilled:
Major criteria
A. Atypical presentation of opportunistic infections or tumor's in patients responding to ART, manifested by any of the following: • Localized disease • Exaggerated inflammatory reaction • Atypical inflammatory response in affected tissues • Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses B. Decrease in plasma HIV RNA level >1 log10 copies/ml
Minor criteria
• Increase in CD4 count after ART • Increase in an immune response specific to the relevant pathogen • Spontaneous resolution of disease with continuation of ART
General IRIS case definition proposed by Robertson, *et al.* (2006)
Required criterion
• Worsening symptoms of inflammation/infection • Temporal relationship with starting antiretroviral treatment • Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease • >1 log10 decrease in plasma HIV load
Supportive criterion
• Increase in CD4+ cell count of ≥25 cells/µl • Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response

Table 1: General case definitions for IRIS [3]

Epidemiology of IRIS

Despite numerous descriptions of the infectious and noninfectious causes of IRIS, the overall incidence of the syndrome itself remains largely unknown [9]. Rep orted incidence varies according to geographic region and by study design [14,15]. The epidemiology of IRIS reflects the epidemiological distribution of HIV-associated OI and the prevalence of various key risk factors in a given population [3]. In a large retrospective analysis examining all forms of IRIS, 25% of patients exhibited one or more disease episodes after initiation of ART [5]. Other cohort analyses examining all manifestations of IRIS estimate that 17–23% of patients initiating ART will develop the syndrome [16]. It is expected that IRIS will become more common in resource-constrained settings, where access to ART is increasing. The underlying prevalence of OI like Mycobacterium tuberculosis (TB) is high in this setting and the patients initiating ART are more likely to have advanced immunosuppression [3]. Reported incidence varied also widely depending associated pathogen; 37.7% of patients with a diagnosis of cytomegalovirus (CMV) retinitis prior to ART initiation developed IRIS, compared to 6.4% patients with a diagnosis of KS [17].

Risk factors of IRIS

Risk factors for the developments of IRIS include an advanced state of immunosuppression and high infective antigen at ART

initiation [6]. Presence of OI at the time of initiation of ART is a clear risk factor for the development of IRIS. Disseminated infection before initiation of ART has also been shown to be associated with increased risk of development of IRIS in patients with TB and cryptococcal disease [3]. A low baseline CD4+ T cell count, below 50 cells/μl, and rapid increase after initiation of ART, higher HIV RNA at ART initiation, rapid decline in viral load are the majors risk factor for both the diseases [9,18]. However, IRIS is known to occur at higher CD4 T-cell counts, suggesting that functional status of the cells also has a role in the pathogenesis of IRIS. Shorter interval between OI therapy initiation and ART initiation, particularly in context of TB-IRIS is associated with a higher risk of IRIS in these patients [1,7]. There may also be a genetic predisposition and certain genes have been associated with an increased susceptibility to the development of IRIS in the presence of mycobacteria and herpes viruses [3]. Male gender and younger age have been inconsistently associated with IRIS [7].

Pathogenesis of IRIS

Despite numerous descriptions of the manifestations of IRIS, the immunopathogenesis of IRIS remains only partially understood. Qualitative and quantitative reconstitution of the immune system, host genetic susceptibility and mycobacterial load are supposedly involved in the pathogenesis of IRIS [9,11]. The immunopathogenesis of the syndrome appears to be result of unbalanced reconstitution of effector and regulatory T-cells, leading to exuberant inflammatory response in patients receiving ART [3]. The syndrome is precipitated by the degree of immune restoration following ART. An alternative immunological mechanism may involve qualitative changes in lymphocyte function or lymphocyte phenotypic expression. For instance, following ART an increase in memory CD4 cell types is observed possibly as a result of redistribution from peripheral lymphoid tissue. This CD4 phenotype is primed to recognize previous antigenic stimuli, and thus may be responsible for manifestations of IRIS seen soon after ART initiation. After this redistribution, naïve T cells increase and are thought to be responsible for the later quantitative increase in CD4 cell counts [19]. Thus IRIS may be due to a combination of both quantitative restoration of immunity as well as qualitative function and phenotypic expression observed soon after the initiation of ART [9]. The third purported pathogenic mechanism for IRIS involves host genetic susceptibility to an exuberant immune response to the infectious or noninfectious antigenic stimulus upon immune restoration. Although evidence is limited, carriage of specific HLA alleles suggests associations with the development of IRIS and specific pathogens [20].

Disease Specific IRIS and Its Management

Mycobacterium tuberculosis - IRIS: Mycobacterium tuberculosis (TB)-IRIS is a paradoxical worsening or recurring of preexisting tuberculous lesions, or a development of new lesions in patients on effective antituberculosis treatment. It may occur during or even after completion of anti-TB therapy [11]. TB is among the most frequently reported pathogen associated with IRIS. It occurs in 15.7% of TB patients starting ART within 2 months of ART initiation [6,9,21]. In patients with miliary or disseminated TB, the occurrence of soft tissue TB-IRIS is more frequent than in those with pleural or lymph node TB [8,11]. TB-IRIS might be misdiagnosed as superimposed infections, treatment failure following inadequate anti-TB treatment, drug-resistant TB, or TB relapse [11]. Clinical manifestations of TB-IRIS include weight loss, fever and worsening of pulmonary symptoms, including development of abscesses, respiratory failure, acute respiratory distress syndrome and death [6,8]. Paradoxical IRIS may occur at any disease site, including lymph nodes, which typically manifests with rapid enlargement followed by suppuration [22]. CNS TB-IRIS typically presents with new or worsening meningitis and/or features of raised intracranial pressure, due to enlarging cerebral tuberculomas or intracranial abscesses, with a high mortality [23].

Condition	Clinical features of IRIS
Pathogen-associated	
Bacteria	
Mycobacterium tuberculosis	Fever, lymphadenitis, new/ worsening pulmonary infiltrates, pleural effusions, hepatomegaly, paradoxical or unmasking TBM/ tuberculoma
NTM	Fever, lymphadenitis (painful/suppurative), pulmonary infiltrates and cavitation, inflammatory masses
Bartonella spp.	Granulomatous splenitis
Chlamydia trachomatis	Reiter's syndrome
Viral	
Herpes viruses	
CMV	Immune recovery uveitis (usually following previous history of retinitis), retinitis (typically unmasking)
VZV	Dermatologic reactivation (shingles), encephalitis, transverse myelitis, stromal keratitis
HSV-1, HSV-2	Mucocutaneous ulceration, encephalomyelitis
EBV	New presentation of non-Hodgkins's lymphoma, Burkitt's lymphoma
HHV-8	Kaposi's sarcoma- IRIS, multicentric Castleman's disease
Hepatitis B, Hepatitis C	Hepatitis flare, rapidly progressive cirrhosis

Condition	Clinical features of IRIS
Polyomaviruses	
JC virus	Paradoxical PML (clinical deterioration, progression of lesions) or unmasking PML (new diagnosis)
BK virus	Meningoencephalitis
Molluscum contagiosum virus	Acute new or recurrent cutaneous papules with florid/ extensive distribution
Parvovirus B19	Pure red cell aplasia, encephalitis
HPV	Warts (acute recurrence/ relapse or enlargement)
Fungal	
Cryptococcus neoformans	Meningitis with raised intracranial pressure,lymphadenitis, pneumonitis, ocular and soft tissue inflammation
Pneumocystis jirovecii	Unmasking PCP, paradoxical deterioration during or shortly after treatment with worsening hypoxia and new pulmonary infiltrates, organizing pneumonia (rare)
Histoplasma spp	Acute fistulous lymphadenopathy
Candida spp	Typically unmasking; mucocutaneous (oral/oesophageal)
Parasitic	
Toxoplasma gondii	New or enlarging intracerebral lesions (ring-enhancing appearance on contrast neuroimaging)
Schistosoma mansoni	Eosinophilia, enteritis, colitis/polyposis
Leishmania sp	
Leishmania major	Cutaneous, uveitis
Leishmania infantum	Post-kala-azar dermal leishmaniasis, visceral leishmaniasis
Leishmania braziliensis	Cutaneous, mucosal
Strongyloidesstercoralis	Gastrointestinal or disseminated presentation; pneumonitis, enteritis, eosinophilia, hepatitis
Cryptosporidium spp	Terminal ileitis, duodenitis, cholangitis, gastrointestinal ulceration
Microsporidium spp	Keratoconjunctivitis
Non-pathogen-associated	
Autoimmune	May occur as a new presentation, or an exacerbation of existing autoimmune condition
Grave's disease	
Guillain -Barré Syndrome	
Rheumatoid arthritis	
Polymyositis	
SLE	
Relapsing polychondritis	
Dermatological	Inflammatory presentation
Eosinophilic folliculitis	
Seborrheic dermatitis	
Pruritic papular eruption	
Acne	
Other	
Sarcoidosis	New or recurrent granulomatous inflammation, typically late (around 12 months post-ART initiation) in patients with CD4 counts .200 cells/mm3; typically pulmonary presentation, but may be cutaneous (erythema nodosum, papular lesions) and/or intra-abdominal
Lymphoid interstitial pneumonitis	Fever, respiratory distress, negative microbiological tests (may mimic PCP)
CNS IRIS	Leukoencephalopathy, demyelination, cerebral edema

Table 2: Pathogens and key clinical features of associated IRIS [1]

It may also present with epidural abscesses, spondylitis, and radiculomyelopathy [24]. Tuberculous meningitis is the most severe form of TB with a poor prognosis in HIV-infected persons, independently of ART use. Neurological TB-IRIS contributes to this poor outcome [11]. Abdominal TB-IRIS can occur as granulomatous hepatitis, retroperitoneal lymphadenopathy, and peritonitis,

whereas the musculoskeletal form manifests as mono- or polyarthritis [6,9,11]. Clinical features associated with different forms of IRIS are summarized in Table 2 and described in more detail in subsequent sections. There is no consensus yet on the standard treatment of TB-IRIS. Approximately half of the cases of lymph node TB-IRIS resolve spontaneously [25]. In some patients with lymph node, air- ways or soft tissue TB-IRIS, prolonged antituberculosis treatment may be required. However the optimal treatment duration is unclear. Most patients with TB-IRIS show clinical improvement in the two months following antituberculosis treatment [11]. Depending on sites and severity of TB-IRIS, adjunctive therapy may be necessary. For instance, patients with soft-tissue abscesses or symptomatic pleural effusions often require aspiration [26]. Systemic corticosteroid administration for four–six weeks improves the outcome of certain forms of TB-IRIS (symptomatic enlarging intracranial tuberculoma, endobronchial obstruction) and reduces proinflammatory cytokines [8,11]. In addition to corticosteroids medications such as thalidomide, hydroxychloroquine and TNF-α inhibitors are under investigation as possible anti-inflammatory agents in the treatment of IRIS. In all cases of IRIS, regardless of the OI involved, ART should be continued unless there is risk of permanent sequelae from continuation or the patient's life is in danger [27]. The timing of the start of the ART is crucial in preventing paradoxical IRIS. WHO recommends that ART be initiated as soon as TB therapy is tolerated by the patient? Ideally, this may be as early as 2 weeks and not later than 8 weeks [3].

Atypical mycobacterial – IRIS: In addition to TB, atypical mycobacteria are also frequently reported as causative pathogens in IRIS. Mycobacterium avium complex (MAC) remains the most frequently reported atypical mycobacterium. MAC-IRIS occurs in about 3.5% of HIV-infected patients treated with ART, and 20% of MAC-IRIS is fatal [3]. It usually presents as either focal or diffuse lymphadenitis, occurring typically within 3 months of initiation of ART, and often with suppuration. MAC related IRIS rarely presents as focal pulmonary disease [4,8,9]. Sometimes, the lungs are involved, with pulmonary infiltrates apparent on chest X. Typically, the onset of this syndrome occurs usually in the setting of substantially increased CD4 counts in a patient whose pre-ART absolute CD4 T-cell count was <50 cells/μL. Histological examination of MAC-IRIS lesions shows well-formed granulomas and few MAC organisms [28]. Treatment is similar to TB-IRIS. Occasionally, surgical excision of profoundly enlarged nodes or debridement of necrotic areas is anecdotally reported. Needle aspiration is another option for enlarged, fluctuant, and symptomatic nodes [9].

Cryptococcal – IRIS: Paradoxical cryptococcal (C)-IRIS is reported to occur in 13%-45% of HIV-infected persons who start ART after treatment for cryptococcal meningitis (CM). It occurs a median of 4-9 weeks following ART initiation but delayed cases have been reported up to a year after initiation of ART [6]. The risk of developing C-IRIS is increased in individuals who have high CSF fungal burdens during the initial episode of CM, and in those who fail to clear the infection prior to the initiation of ART [29]. C-IRIS manifests frequently as a multiorgan disease process, affecting the brain, lungs and skin; and while C-IRIS usually involves meningeal disease [6,8]. It can be manifested in many other different ways as lymphadenitis and pneumonitis [4,6]. CM-IRIS typically presents with headache and new CNS signs, such as raised intracranial pressure, impaired consciousness, seizures, and focal neurology in a patient with previously diagnosed CM who has initiated ART and has a substantial rise in CD4 T cell count [30,31]. Diagnosis of paradoxical CM-IRIS is based on INSHI criteria including increased white blood cell counts in cerebrospinal fluid (>50 cells/Ml), persistently raised intracranial pressure refractory to therapy, rapidly expanding CNS lesion [6]. In CM-IRIS, mortality rates have ranged between 8% and 30% [20]. In fact, according to some investigators, the morbidity and mortality rates have actually increased in CM-IRIS [31]. The antifungal regimen should be intensified in patients experiencing complications of C-IRIS and raised intracranial pressure can be controlled with therapeutic CSF drainage by lumbar puncture [5]. Corticosteroids can be considered in severe cases. Guidelines for CM now suggest clinicians wait 4-6 weeks after commencing amphotericin B-based CM treatment, before ART is initiated in CM patients [6,8].

Kaposi Sarcoma-IRIS: Given the known associations of Kaposi sarcoma (KS) with human herpes virus-8, it is not surprising to observe these cancers occurring or worsening in the context of IRIS. Paradoxical KS-IRIS occurs in 7%-31% of cases. Onset is between 1 and 22 weeks, and usually in the first 12 weeks post-ART initiation [32]. Increased susceptibility to KS-IRIS correlates with a rapid rate of CD4 T-cell increase during ART, as well as peripheral oedema consistent with advanced-stage KS [33]. Little is known about the pathogenesis of KS-IRIS. Proinflammatory and Th1 cytokines are considered to be important in KS pathogenesis. Increased KS-IRIS risk is associated with use of ART alone as initial KS treatment, more extensive baseline KS tumor stage, baseline plasma HIV-1 RNA more than 105 copies/mL, and baseline detectable plasma HHV-8 DNA [34]. KS-IRIS manifests with inflammation or enlargement of existing lesions, appearance of new lesions or the development of lymphoedema [3]. KS-IRIS is noted to have high morbidity and mortality, especially in the setting of visceral disease, which frequently affects the lungs and gastrointestinal tract [35]. Treatment for KS-IRIS includes systemic chemotherapy and supportive measures. Radiotherapy should airway obstruction occur. Liposomal anthracyclines (doxorubicin) are the preferred first-line chemotherapeutic agents for KS and may be indicated in KS-IRIS where available. Corticosteroids may be harmful as there is an association with acute progression of KS lesions. ART should be continued. The timely initiation of ART remains the best strategy to avoid the development of these malignancies. Use of systemic chemotherapy for extensive disease prior to ART initiation may also help prevent KS-IRIS [36].

Cytomegalovirus infection- IRIS: 37.7% of patients with a diagnosis of cytomegalovirus (CMV)-retinitis prior to ART developed IRIS [37]. CMV reactivation is associated with advanced immune suppression (CD4 count below 50 cells/mm3) [6]. It may be seen either in patients with a prior history of CMV retinitis or in patients with no previous evidence of retinitis [37]. In addition to classical CMV retinitis, ART led to new clinical manifestations of the infection: immune recovery vitritis (IRV) and immune

recovery uveitis (IRU), seen exclusively in people with previous CMV retinitis infection who responded to ARV therapy [9]. There are currently no defined criteria for immune recovery uveitis (IRU); nevertheless it is recognized in HIV infected patients with CMV retinitis who develop new or increased noninfectious intraocular inflammatory reactions a few weeks after ART initiation [37]. Treatment of CMV-IRIS involves anti-CMV therapy with gancyclovir. The treatment can be switched to valganciclovir per os after two weeks of intravenous treatment after demonstrating patient's clinical and radiological improvement; keeping the therapy until the maintenance of the CD4+ T-cell count is above 100 for 3-6 months [38]. However, IRU may not respond to anti-CMV therapy. The use of systemic corticosteroids has been successful, and IRV may require periocular corticosteroid injections [3, 9].

Progressive Multifocal Leukoencephalopathy –IRIS: Progressive Multifocal Leukoencephalopathy (PML)-IRIS, an OI caused by the human JC virus, a polyoma virus, has been reported in 18% of PLHIV with PML [39]. It usually occurs within 1-2 months of ART. In addition to atypical clinical findings, the presence of neuroimaging abnormalities, not classic for untreated PML makes PML-IRIS more recognizable than IRIS associated with some other opportunistic diseases. PML-IRIS is characterized by the development of contrast enhancement of the PML lesions as well as mass effect and increased high FLAIR/T2 signal due to interstitial edema [31]. Some PML-IRIS cases are mild and resolve with continued ART, other cases may lead to significant morbidity and even mortality because of a severe inflammatory response. In fact, in 2 cases, PML-IRIS proved fatal after only 2 weeks of ART [40]. The role of corticosteroids in PML-IRIS is not clear [3]. A recently published case report described use of maraviroc, a CCR5 antagonist, in an HIV-uninfected patient with PML-IRIS, with a favorable outcome, but efficacy has not yet been assessed in a clinical trial [6].

Pneumocystis jiroveci pneumonia-IRIS: Pneumocystis jirovecii (P. Jirovecii) is a common fungal cause of IRIS [6]. Pneumocystis jiroveci pneumonia (PCP) - IRIS tends to present early, at a median 15 days after initiation of ART. PCP-IRIS presents as a worsening of existing PCP or unmasking of a previously asymptomatic infection [8]. It may present as worsening pulmonary symptoms (dyspnoea, worsening hypoxia and increased inflammatory cells on bronchoscopy) and high fever [41]. Chest X-ray may show worsening lung involvement and oxygen saturation or arterial blood gas measurements may show worsening hypoxia or alveolar-arterial oxygen gradient. PCP IRIS, in certain cases, may lead to fatal acute respiratory failure [9]. The development of PCP-IRIS after discontinuation of steroid therapy suggests a role for the reintroduction of steroids in these patients [3]. In cases of PCP-HIV co-infection, it is recommended that ART be started within 2 weeks of treatment of OI, based on a study that evaluated early ART and deferred ART [8].

Varicella zoster virus infection-IRIS: With the introduction of protease inhibitors, increasing rates of herpes zoster were noted in HIV-infected patients. Incidence rates are three to five times higher than the observed in the pre- ART era. Mean onset of disease from ART initiation was 5 weeks (range 1-17 weeks) [42]. Although complications such as encephalitis, myelitis, cranial and peripheral nerve palsies, and acute retinal necrosis can occur in HIV infected patients, the vast majority of patients exhibit typical or atypical dermatomal involvement without dissemination or systemic symptoms [9]. Acyclovir is beneficial in IRIS-associated zoster [3].

Sarcoidosis – IRIS: Patients may present with manifestations of autoimmune disease following initiation of ART. The reported associations are limited to case reports. Sarcoidosis is recognized as potential complication of immune reconstitution [43]. It has been reported in several patients on ART, and needs to be distinguished from IRIS associated with mycobacterial pathogens [41]. IRIS can induce sarcoid-like lesions in tissues within the first few weeks of initiating therapy [44]. The clinical manifestations and histological features are similar to patients without HIV [41]. Respiratory and constitutional symptoms are common, occurring in approximately 50%. Extrathoracic involvement is also frequent, and sarcoidosis can involve almost any organ, including the eyes, skin, spleen, liver, heart, peripheral lymph nodes, nervous system and salivary glands. Hypercalcaemia may also be encountered. Pulmonary manifestations include restrictive and obstructive ventilatory defects with decreases in the diffusing capacity on pulmonary function testing. CXR findings include parenchymal opacities, which can include small micronodules, ill-defined lesions, cavitatary nodules or cysts. Hilar and mediastinal lymphadenopathy are common [45].

Prognosis of IRIS: Mortality associated with IRIS is relatively uncommon; however, associated high morbidity places considerable burden on the healthcare system. Morbidity and mortality rates vary according to the pathogen and organs involved [4]. Overall mortality in IRIS is reported to be between 0% and 15%, with variability attributed to geography, associated OI, baseline morbidity, and degree of immunosuppression. IRIS affecting the central nervous system (CNS) confers a particularly high mortality [4]. High mortality rates are reported for cryptococcal meningitis. Overall mortality rate of TB-IRIS is low [46].

Treatment of IRIS: Treatment of IRIS involves optimal treatment of the underlying pathogen to reduce antigen load; supportive measures; and, in some cases, immunosuppression with corticosteroids. Systemic corticosteroid use is associated with a number of potential adverse effects in HIV, including infective complications, such as reactivation of herpes virus infections, KS progression, and mucocutaneous candidiasis [47]. Additionally, non-infective conditions are associated with chronic oral corticosteroid use, including hyperglycemia, hypertension osteoporosis, and gastrointestinal ulceration. Therefore, aside from cases of TB-IRIS, systemic corticosteroids are recommended for more severe forms of IRIS inflammation, in the absence of contraindications, and more commonly for mycobacterial and fungal-associated IRIS than for viral-associated IRIS [6].

Prevention of IRIS: The diagnosis of OI before the start of ART is important for the prevention of IRIS [8]. Patients with high risk features for the development of IRIS should be identified. In the presence of OI, the benefit of reducing the likelihood

of IRIS by deferring ART must be balanced with the risk of delaying ART, particularly in patients with advanced disease [3]. Prevention strategies include: treatment of HIV before advanced immunosuppression develops; OI prevention in advanced HIV (cotrimoxazole to prevent PCP); and optimal timing of ART initiation. This varies according to pathogen and CD4 count and takes into account mortality and IRIS risk [6].

The development of IRIS is based on the presence of residual antigens from opportunistic infection during recovery. Therefore, the diagnosis and treatment of OI before the start of ART is important for the prevention of unmasking form of IRIS. Screening all patients for possible OI before starting ART initiation is recommended [8]. A detailed evaluation should be done: complete blood count with differential, serum electrolytes, erythrocyte sedimentation rate (ESR), liver function tests and renal function tests, CD4+ count and HIV viral load, chest X-ray, Mantoux (tuberculin) test, sputum stain and culture, and ultrasonography of abdomen. Ophthalmologic examination should be included in all patients [9]. While ART initiation causes IRIS, it is key to recovery of immune function and improved health outcomes, therefore delay or discontinuation of ART due to IRIS is not usually recommended. A notable exception is in patients with CM, in whom ART should be delayed until 4-6 weeks after CM treatment initiation.

Conclusion

Clinicians treating HIV infected patients need to be aware that ART-engendered immune recovery may result in pathological inflammation in a subset of patients. Vigilance needs to be especially high during the first several months of therapy when the incidence of IRIS peaks, but cases continue to occur even after 1 or 2 years of therapy. More studies are needed to elucidate the pathogenesis and establish better treatment modalities.

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