Immune reconstitution inflammatory syndrome

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INTRODUCTION

Antiretroviral therapy (ART) strengthens the immune system and restores protective pathogen-specific immune responses. This results in decreased incidence of opportunistic infections (OI), decrease in the viral load and increase in the CD4 counts. With restoration of immunity, the body begins to fight aggressively against coexisting infection thereby causing atypical manifestations of opportunistic infections, which may cause severe inflammation in tissue. The constellation of clinical symptoms, signs or investigational parameters resulting from such inflammatory response has been variously called immune reconstitution inflammatory syndrome (IRIS) or immune restoration disease (IRD) or immune rebound illness.[1]

IRIS is defined as occurrence or worsening of clinical and/or laboratory parameters despite a favorable outcome in human immunodeficiency virus (HIV) surrogate markers (CD4 counts) and plasma viral load.[2] Both infective (clinical or subclinical) and noninfective conditions can act as triggering factors for precipitating IRIS.

HISTORY OF IRIS

After the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, there were a lot of case reports and case-series dealing with IRIS[3,4] and the name IRD was given for the phenomenon prior to 2000.[5] Joseph A. De Simone and colleagues from Thomas Jefferson University in Philadelphia were one of the first groups who attempted to define immune reconstitution syndrome in 2000.[6] They found that many HIV-positive people developed a spectrum of illnesses once they responded to HAART. They developed conditions such as *Mycobacterium avium* complex (MAC) infection and cryptococcal meningitis, at a time when their immune function was actually improving. Initially it was considered to be a Jarisch-Herxheimer or lepra-like reaction. Later it was found to be due to the restoration of immunity thereby eliciting hypersensitivity reaction to an existing microbe or antigen in the body. De Simone and his colleagues named this relatively uncommon phenomenon as immune reconstitution syndrome.[6]

RISK FACTORS FOR IRIS

IRIS occurs more frequently in some patients or in some situations. These include: a CD4 count below 50 cells/cmm prior to initiation of HAART,[7] a high viral load before initiation of therapy,[8] undetected presence of antigens of nonviable microorganisms (e.g., cryptococci and CMV), active or subclinical infection by opportunistic pathogens, initiation of ART in close proximity to the diagnosis and initiation of treatment

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for an OI,[9] use of cytokines such as IL-2 to treat HIV infection and genetic mutations of innate cytokines.

CRITERIA FOR DIAGNOSIS

Recently, French *et al* have laid down criteria so as to aid the diagnosis.[2] These are:

Major criteria

1. Atypical presentation of 'opportunistic infections or tumors' in patients responding to antiretroviral therapy.
2. Decrease in plasma HIV RNA level by at least $1\log_{10}$ copies/mL.

Minor criteria

1. Increased blood CD4 T-cell count after HAART.
2. Increase in immune response specific to the relevant pathogen, e.g., DTH response to mycobacterial antigens.
3. Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of antiretroviral therapy.

MECHANISM OF IRIS

Although the exact mechanism of IRIS is not known, it may be due to immunologic consequences of HAART such as increase in CD4 cell levels, along with an elevated CD8 cell count and an increased activity of cytokines like IL-2 and interferon-gamma.

De Simone and his colleagues noted that a decrease in HIV viral load might alter levels of interleukin 12 (IL-12), a mediator of anti-cryptococcal activity, resulting in meningitis symptoms. Guillaume Foulon and colleagues found that interleukin 2 (IL-2) and interferon-gamma appeared to be the important factors in two patients developing sarcoidosis as IRIS, as both cytokines are essential in the production of a granulomatous response.[10]

PRESENTATIONS OF IRIS

The clinical features of IRIS differ according to the inflammatory or infective pathology that is responsible for causing it [Table 1]. Briefly the various presentations include,

Noninfectious syndromes:

(i) ***With cutaneous involvement***: Papular urticaria, eosinophilic folliculitis, Sweet's syndrome, Reiter's syndrome, sarcoidosis, systemic lupus erythematosus, Peyronie's disease

(ii) ***Without cutaneous involvement***: Autoimmune thyroiditis, Guillain-Barré syndrome, myopathy, radiculopathy, acute porphyria, Non-Hodgkin's lymphomas, Castleman's disease

Infectious syndromes

Various infectious syndromes described in association with IRIS are mentioned in Table 1.

CLINICAL FEATURES OF SOME COMMON IRIS

The clinical manifestations of IRIS associated with some common OIs are elaborated below.

Tuberculosis and atypical mycobacterial infections[11,12]

Tuberculosis (TB) as IRIS typically occurs one to six weeks after the patient begins ART. The signs and symptoms of tuberculous IRIS may include high fever, new or worsening lymphadenopathy (mediastinal or peripheral), worsening of pulmonary symptoms and infiltrates or new or increasing pleural effusion. Lymph node abscesses usually occur during the first weeks on HAART.

Extrapulmonary presentations may occur, including expanding central nervous system lesions, skin or visceral abscesses, osteomyelitis, nephritis, meningitis, hypercalcemia, hepatosplenomegaly, epididymo-orchitis, psoas abscess and bowel perforation.

In one study, four out of five patients, who had clinically developed atypical mycobacterial infections after HAART and significant improvements in CD4 T cell levels, showed a significantly increased MAC-specific T cell response *in vitro*, proving that this phenomenon is indeed caused by the unmasking of subclinical infections.

Table 1: Features of infectious immune reconstitution inflammatory syndrome

Infective agent	Clinical features
Bacterial infections	
Mycobacterium tuberculosis (within one to six weeks after ART)	Lymphadenopathy, high fever, cough, dyspnoea, edema, serositis, pneumonitis, hepatosplenomegaly, epididymo-orchitis, psoas abscess, bowel perforation, arthritis, nephritis, osteomyelitis, expanding CNS lesions
MAC (within one to three months after ART)	High fever, lymphadenitis (paraaortic and mesenteric), lung infiltrates, bursitis, myositis, osteomyelitis, abscess, skin nodules, adrenal insufficiency, hypercalcemia
Mycobacterium leprae	Type I lepra reaction
Bartonella species	Bartonellosis
Viral infections	
VZV (within first four months of ART)	Herpes zoster
HSV	Recurrent oroanogenital herpes, Kaposi's sarcoma
CMV (within one to two months after ART)	Retinitis, vitritis, uveitis, cytoid macular edema, CNS (dementia, radiculomyelopathy, encephalitis), pancreatitis, lung, colon, skin
HIV	Demyelinating leukoencephalopathy
Parvovirus B19	Encephalitis
HPV	Inflamed warts
Molluscum contagiosum virus	Inflamed mollusca
Hepatitis C / Hepatitis B virus	Hepatitis
JC virus	Progressive multifocal leukoencephalopathy
Fungal infections	
Histoplasma capsulatum	Histoplasmosis
Cryptococcus neoformans	Meningitis, abscess, cavitary pneumonia, palsy
Candida albicans	Candidiasis
Protozoal and parasitic infections	
Pneumocystis jiroveci (within one week to 11 months after ART)	ARDS, severe hypoxia
Toxoplasma gondii	Encephalitis
L. donovani	Leishmaniasis

ART - Antiretroviral therapy, CNS - Central nervous system

Cryptococcal meningitis[13]

Cryptococcal IRIS is usually seen within one week to 11 months after ART. In patients with or without previously diagnosed cryptococcal meningitis, presentation of cryptococcal IRIS typically includes fever, headache, lymphadenitis and meningitis. In cases of IRIS, the MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. Cryptococcal antigen in the cerebrospinal fluid is positive, although culture remains negative.

***Pneumocystis jiroveci* pneumonia**[14]

Immune reconstitution inflammatory syndrome may present as worsening pulmonary symptoms and high fever in patients who had been improving on PCP therapy or in patients with recent successful treatment of PCP. 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.

CMV[15]

CMV retinitis may be seen either in patients with a prior history of *CMV* retinitis or in patients with no previous evidence of retinitis while *CMV* vitritis and uveitis are seen exclusively in people with previous *CMV* retinitis infection who responded to ARV therapy.

CMV vitritis typically will present with acute onset of blurred vision and "floaters" caused by posterior segment inflammation. Ophthalmologic examination reveals numerous inflammatory cells in the vitreous humor. Symptoms usually resolve in one month without specific treatment and without any lasting visual effects.

CMV uveitis as IRIS may occur within months of ART initiation, but typically is a late complication; occurring about three years after patients begin ART. It often results in macular edema, epiretinal membrane formation and/or cataracts, which can lead to permanent vision loss and hence requires a high index of suspicion.

DIFFERENTIAL DIAGNOSIS

Failure of ART or toxicity, active opportunistic infection and failure of antimicrobial therapy are

considered in the differential diagnosis.

Failure of ART can be ruled out with decrease in CD4 count, increase in viral load, along with clinical deterioration while active opportunistic infections can be ruled out by isolating the pathogens. The World Health Organization (WHO) made an important distinction between IRIS and clinical failure while on anti-HIV therapy.[16]

"Clinical failure is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration. This needs to be differentiated from an immune reconstitution syndrome which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline."[16]

TREATMENT OF IRIS

As of now, there are no standard guidelines for the treatment of IRIS and the following interventions are mostly based on published case reports and other anecdotal clinical evidence. Treatment includes continuation of primary therapy against the offending pathogen in order to decrease the antigenic load, continuation of effective HAART and judicious use of anti-inflammatory agents.[17]

1. Milder IRIS: Continue HARRT, antimicrobial agents and nonsteroidal antiinflammatory drugs.
2. Severe life-threatening IRIS: Needs oral prednisolone, approximately 1-2 mg/kg. The exact duration and dose of the steroid is variable and depends upon clinical severity. Sometimes the duration of the steroid therapy may extend to six months or one year. Consider discontinuation of HAART in case of severe life-threatening IRIS (e.g., encephalitis, ARDS, cerebritis and perilesional cerebral edema).

Patients with IRIS have almost invariably better outcomes than those who are HIV positive with clinical progression of a given disease. The occurrence of IRIS does not require any modification in the treatment of OIs. Maintenance treatment for OIs should not be changed and previously completed OI treatment (e.g., for tuberculosis) should not be reinitiated. Similarly, the dosages of chronic suppressive treatment for an OI should not be increased.

PREVENTION OF IRIS

Diagnosis of IRIS requires a high index of suspicion. Detailed clinical history should be taken in patients suspected to have IRIS, which includes the following: Symptoms: fever, cough or any specific symptoms; history of OIs: including recently diagnosed as well as past OIs; treatment of OIs: date of initiation, duration of therapy, clinical response, adherence, defaulter, resistance; ART initiation: date, regimen, adherence, prior history of ART, toxicity, any drug interaction; CD4 count and HIV viral load prior to ART initiation.

Look for the vital signs, including temperature, heart rate, blood pressure and respiratory rate. Perform a careful and thorough physical examination based on symptoms and suspicion of systems involved. Ophthalmologic examination should be included in all patients.

The following investigations should be considered before starting ART: Complete blood count with differential, ESR, serum electrolytes, 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. In a suspected case, even an initially negative Mantoux test becoming positive could be suggestive of IRIS.

Patients who are started on ART having CD4 count of less than 100 cells/μl require close clinical monitoring during the first weeks of ART. Similarly, they should be counseled about the risk of development of IRIS to avoid being discouraged and defaulting on therapy as development of IRIS suggests increase in the immunity and is a good sign unless life-threatening.

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