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Immune Reconstitution Inflammatory Syndrome

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Background

Soon after the introduction of highly active anti retroviral therapy (HAART) for the treatment of HIV infected immunodeficient patients in mid 1990's it was noticed that few patients had "paradoxical" deterioration in the clinical symptoms, despite having decreasing HIV- RNA and rising CD4+cell count[1,2]. Initially this was attributed to progression of the opportunistic infection (OI) for which the patient was being treated or due to a new OI or as a result of drug toxicity. Subsequent investigations revealed that on HAART, there was restoration of pathogen specific immune response which mounted an inflammatory response against the clinically manifest OI or against a subclinical OI leading to worsening of symptoms and deterioration in the clinical condition of the patient in spite of immunological recovery. This immunopathological syndrome has been variously named as Immune Reconstitution Inflammatory Syndrome (IRIS), Immune Reconstitution Syndrome (IRS), Immune Reconstitution Disease (IRD), Immune related disease, Immune Rebound illness, or HAART attack etc[1,2]. Although IRIS is now a well established entity there continues to be uncertainty regarding its pathogenesis and management and still there is lack of a well accepted criterion for the diagnosis of the condition. As the use of HAART is increasing around the world, more so in the developing countries where the prevalence of HIV- OI co infection is quiet high, incidence of IRIS is likely to increase.

Historical Perspective

The immunopathological inflammatory response is reminiscent of similar clinical worsening seen in occasional non HIV patients being treated for tuberculosis (suppuration and enlargement of lymph nodes or worsening of symptoms of tubercular meningitis) or leprosy (type 1 lepra reaction). Similarly the clinical worsening in some patients following bone marrow transplantation also has the immuno inflammatory basis.

Among HIV infected patients such inflammatory response was first recognized on Zidovudine monotherapy[3]. Patients developed atypical localized presentation of *Mycobacterium avium* complex (MAC) infection characterized by fever and painful lymph node enlargement with suppuration and restoration of Delayed type hypersensitivity (DTH) to mycobacterial antigen in contrast to the classical systemic disease produced by MAC with loss of DTH[4]. Following introduction of HAART when immune restoration was robust, numerous cases were reported and now it has been established as a well defined clinical syndrome. The recognition of the syndrome which is the consequence of a successful, but undesirable, effect of HAART is at times difficult considering its myriad presentation. The exact magnitude and spectrum of the problem can only be discerned after a precise diagnostic criterion is defined and large series are reported.

Incidence

The estimates of the incidence of IRIS are derived from small samples and vary from 4-45%. Most of the reports are from developed countries. With the availability of generic HAART, it is now being increasingly used in developing countries where there is high co prevalence of OI. Incidence of IRIS is likely to increase. Although in a study reported from India where incidence of IRIS was studied in HIV – Tuberculosis co infection, the incidence of IRIS was 15.2 cases per 100 patient years only[5].

Majority of patients develop IRIS within 60 days of initiation of HAART and most cases in first three months of therapy[6], but it can be seen up to 2 years of initiating HAART[7].

Diagnosis and definition: In an HIV infected patient with low $CD4^+$ cell count and undiagnosed OI, initiation of HAART may unmask the infection or can present atypically suggesting IRIS (localized MAC infection). While an HIV infected patient with known OI on initiation of HAART, the patient may have three different fates; 1) may have asymptomatic immune recovery i.e., OI is controlled and patient becomes asymptomatic, 2) may develop a new symptom attributable to new OI, medication side effect or IRIS or 3) may have return to the original symptoms of OI after initial recovery suggesting progression and/or relapse of OI or IRIS. In few of the patients the immune recovery may trigger an autoimmune disease or can flare the existing autoimmune disease (Systemic lupus erythematosis or Graves disease) or can lead to a sarcoid like granuloma. Thus IRIS can be classified as[8,9]:

1. Infectious IRIS
2. Autoimmune IRIS
3. Sarcoid IRIS

The diagnosis of IRIS is a diagnosis of exclusion and in wake of immunological recovery (decrease in HIV-RNA and/or increase in CD4+ cell count), worsening of the clinical symptoms in a patient receiving HAART, IRIS is diagnosed only after ruling out active or new OI and also after excluding drug toxicity. The proposed criteria for diagnosis of IRIS which takes these factors in cognizens are as follows[4,9]:

Major criteria

A. Atypical presentation of opportunistic infections or tumors
   a. Localized disease, e.g. Lymph nodes , spleen, liver
   b. Exaggerated inflammatory reaction, e.g.
      i. Severe fever, with exclusion of other causes
      ii. Painful lesions
   c. Atypical inflammatory response in affected tissue, e.g.
      i. Granulomas, suppuration and necrosis
      ii. Perivascular lymphocytic infiltrates
   d. Progression of organ dysfunction or enlargement of pre-existing lesion after definite clinical improvement with pathogen specific therapy prior to commencement of HAART and exclusion of treatment related toxicity and new infection.
      i. Development or enlargement of space occupying lesion after treatment of cerebral cryptococcosis or toxoplasmosis
      ii. Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary MTB or PCP
      iii. New onset or worsening of uveitis after resolution of CMV retinitis
      iv. Fever and cytopenia after treatment of MAC
      v. Enlargement of Kaposi's sarcoma lesion and subsequent resolution without specific therapy

B. Decrease in plasma HIV RNA by ≥ 1 log.

Minor criteria

a. Increased CD4+ cell count
b. Increase immune response specific to reactive antigen, eg. DTH to Mycobacterial agent
c. Spontaneous resolution of disease without specific therapy.

The diagnosis of IRIS requires presence of both major criteria or criteria A of major and two of minor criteria.

Risk factors for IRIS: Identification of risk for development of the syndrome may help in its prevention. The following risk factors has been identified from the data accumulated over the last decade[4,10].

1. Active or subclinical OI or the antigen of a non viable microorganism (e.g. Cryptococcal or CMV),
2. CD4+ cell count less than 50/ml (a marker of high pathogen load),
3. Early initiation of HAART close to the time of initiation of therapy for OI,
4. Rapid HIV-RNA level suppression during first three month of therapy and
5. Disease susceptibility genes which has been identified for certain IRIS e.g. HLA-B44, -A2, -DR4 associated with herpes virus IRIS.

Pathogenesis: Exact mechanism is not known, but it is believed that these reactions are often caused by excessive responses by the recovering immune system[4,10]. HAART improves both the qualitative and quantitative immune defects that lead to improvement of pathogen-specific immunity, a phenomenon of which current understanding is limited. OIs are basically random events occurring primarily in patients with advanced HIV with CD4+ cell counts below 200. The patient may have been exposed to many different pathogens, but usually only manifests active infection with one at a time - although later on, he or she may

develop another active infection in quite a random order. The infectious IRIS has two pattern of presentation. Early IRIS presents within first three month of HAART and appears to result from immune response against viable opportunistic pathogen which are often subclinical infection. Late IRIS can present months to years after commencing therapy and results from immune response against non viable opportunistic pathogen. The potential for variability in one patient is wide and may be influenced by genetic factors. Questions like at what point does a patient's improved immunity interact with pathogens and why do only some patient develop IRIS are still unanswered.

Infectious IRIS

- Tuberculosis IRIS: Tuberculosis IRIS is the most commonly occurring IRD syndrome worldwide.[11] It nearly always presents with mediastinal and/or peripheral lymphadenopathy and fever. The lymph nodes are often tender. Other clinical findings may include cough, dyspnea, ascitis, hepatosplenomegaly, epididymo-orchitis, worsening infiltrates or new pleural effusion on chest X-ray, skin or visceral abscesses, arthritis, and osteomyelitis[8]. Typically, the onset of the syndrome occurs 1 to 8 weeks after HAART is initiated in an HIV-infected patient who is already on treatment for active tuberculosis. AFB smear and culture are usually negative and are often associated with CD4+ rise and PPD conversion.
- MAC IRIS: MAC IRIS usually presents as lymphadenitis (often hilar, retroperitoneal, or cervical), nearly always accompanied by high fever. Sometimes, the lungs are involved, with pulmonary infiltrates apparent on chest X-ray[4,11]. There have been reports of localized bone, joint, skin, soft tissue, prostate and brain lesions. Typically, the onset of this syndrome occurs 1 to 12 weeks after HAART initiation, usually in the setting of substantially increased CD4+counts in a patient whose pre-ART absolute CD4+T-cell count was <50 cells/μL. Blood cultures for MAC are usually negative. Histological examination of MAC IRIS lesions shows well-formed granulomas and few MAC organisms[4].
- CMV IRIS: Three IRIS syndromes associated with CMV end-stage organ disease have been described. CMV retinitis IRIS presents as a new opacified retinal lesion, often at the site of a previously noted retinal lesion in patients with a prior diagnosis of CMV retinitis, usually 1-2 months after HAART has been initiated and the absolute CD4+T-cell count has risen to >50 cells/μL from a pretreatment value of <50 cells/μL[12,13]. CMV IRIS retinitis appears identical on exam to the active OI, i.e. CMV retinitis (caused by uncontrolled CMV replication with retinal cytopathic effect). The diagnosis of CMV retinitis IRIS is therefore a clinical one, based on appropriate setting (a recent increase in CD4+T-cell count) and supported by frequent ophthalmologic exams (e.g. every 2 weeks) that reveal clearing of the lesions without introduction or change in anti-CMV therapy. In contrast, retinal lesions caused by uncontrolled CMV replication (e.g., due to antiviral drug-resistant CMV) will generally increase in size, or new lesions will occur, within a month of follow-up if there is no change in anti-CMV therapy.
- CMV vitritis IRIS is a benign, but frightening, syndrome. Patients with a preexisting diagnosis of CMV retinitis who are receiving anti-CMV therapy present with acute onset of visual blurring, usually 1-2 months after HAART has been initiated and the absolute CD4+ T-cell count has risen to >50 cells/μL from a pretreatment value of <50 cells/μL. Ophthalmologic exam reveals extensive infiltration of the vitreous humor with inflammatory cells, which is the cause of the blurred vision. The condition usually resolves without any specific intervention within 1 month, without residual visual morbidity.
- CMV uveitis IRIS is a late complication of immune reconstitution that occurs a median 3 years after HAART is initiated in patients who have a prior history of CMV retinitis[14]. The uveitis primarily involves the posterior pole of the eye and is usually painless. This IRIS frequently leads to macular edema, epiretinal membrane formation, or cataract, and usually results in permanently impaired visual function. There is no evidence that reinitiation of anti-CMV therapy or intraocular injection of corticosteroids is beneficial in preventing or altering the course of CMV uveitis IRIS.
- Cryptococcal IRIS: Cryptococcal meningitis IRIS typically presents with headache and new meningeal signs and symptoms in a patient with previously diagnosed cryptococcal meningitis who has initiated HAART and has had a substantial rise in CD4+T-cell count[15]. The onset has been reported to occur from 1 week to 11 months after initiating HAART. Many patients have had increased white blood cell counts (primarily lymphocytes) in their cerebrospinal fluid (CSF) at the time of IRIS diagnosis. (CSF white blood cell counts are not typically elevated in AIDS-related cryptococcal meningitis.) Lymphadenitis,

particularly involving the mediastinum, has been reported in cryptococcal IRIS, and granulomatous inflammation leading to hypercalcemia also can occur.

- Other IRIS: Localized herpes zoster has been reported to occur with increased frequency within the first 4 months after initiating HAART[4,9,16]. To date, none of the reported cases have been disseminated disease, and patients generally have responded well to acyclovir therapy. Published case reports of encephalitis have been suggestive of an IRIS based on temporal association with HAART initiation and subsequent rise in CD4+counts and, in some cases, biopsy results. Progressive multifocal leukoencephalopathy[17], parvovirus B19 infection, central nervous system CMV or herpes simplex virus infection, Leprosy IRD and disseminated MAC infection each have been reported. Patients with severe, active Pneumocystis pneumonia who were improving on antipneumocystis therapy and adjunctive corticosteroids developed acute respiratory failure with fever after early introduction of HAART[18]. As an adverse effect of HAART hepatotoxicity occurs in patients with HBV and HCV coinfection. HAART associated hepatotoxicity in HIV/HBV coinfected patients is associated with a decrease in plasma HIV RNA level and increase in CD4+ counts. Some patients clears HBeAg and HBV DNA[19]. While in others it is associated with increase in plasma levels of HBV DNA or reappearance of HBsAg. Explanation to this dichotonomous immunological and virological effects of HAART in HIV/HBV coinfected patients is not clear.

Non infectious IRIS: It includes Autoimmune IRIS and Sarcoid IRIS[9,20].

Auto-immune thyroid disease may be a late manifestation of immune reconstitution in HIV-positive patients taking HAART, and immune dysregulation may be an important factor. It may be presenting for the first time or there may be exacerbation of the existing disease. Systemic lupus erythematosus, Guillain barre syndrome, Rheumatoid arthritis, Immune thrombocytopenia as well as Grave's disease has been reported.

Case series of sarcoidosis occurring with rise in CD4+ T-cell count in patients on HAART have been reported. The clinical presentation was similar to that of sarcoid in non-HIV-infected patients. As Th1-type CD4+T-cell-mediated granuloma formation is central to the immunopathogenesis of sarcoid, it is reasonable to consider such HAART-related sarcoid cases as a form of IRIS[20].

Treatment of IRIS: There are no standard guidelines for the management of IRIS. It is important to note that most reported IRIS cases have resolved within some weeks simply by continuing HAART and treatment of the opportunistic pathogens. Unless clinical presentation of the IRIS is immediately life threatening, there is no rationale for discontinuing HAART[3,4].

A brief course of systemic prednisone (e.g.1 mg/kg/day for 1-2 weeks followed by a slow taper) can be used in severe cases[5]. Discontinuation of HAART can be considered if inflammatory responses are life threatening (e.g. Intracranial IRIS leading to encephalitis, cerebritis, perilesional cerebral edema, pulmonary IRIS with ARDS etc), unresponsive to steroids, or if the involved pathogens are not amenable to specific antimicrobials (e.g. Parvovirus B19, JC virus).

Occurrence of IRIS does not require reinitiation of antimicrobial treatment, or change in existing maintenance therapy, for the infection in question. For example, if a full course of Tuberculosis treatment already has been completed when IRIS occurs, re-treatment for Tuberculosis is not indicated[9].

There are some clinical management questions for which there is little or no evidence to help with decision making. Should HAART be delayed or administered immediately to patients who have acute, severe OIs with associated high mortality risk (e.g. severe Pneumocystis pneumonia requiring intubation or cryptococcal meningitis with altered mental status and high CSF pressure)? It is possible that immediate immune restoration might have a beneficial effect on survival, but it is equally possible that such immune restoration could lead to an increased inflammatory response that could increase mortality[2]. In medically stable patients who are responding to therapy for recently diagnosed OIs, it is not known whether HAART should be initiated immediately to reduce risk of subsequent mortality and development of other OIs or delayed by 4, 8, or 12 weeks with the intention to reduce the risk of IRIS[4,6]. There is some data from observational studies of cryptococcal meningitis, tuberculosis, and disseminated MAC suggesting that delaying HAART for 4-8 weeks after initiating antimicrobial therapy for the OI is associated with a decreased risk of IRIS. For CMV disease, there appears to be no rationale for delaying HAART, because the early CMV IRD syndromes (retinitis and vitritis) are benign and do not lead to long-term visual morbidity. It is hoped that future randomized trials will answer some of these questions.

CONCLUSION

IRIS is a consequence of immune reconstitution in HIV patients after initiating HAART, especially when the patients are severely immuno-compromised at the initiation of therapy. This situation is quiet common in developing countries where the patient present late and treatment is started when the patient is severely immunocompromised. The spectrum of IRIS is likely to vary in different geographical area and will be determined by the prevalence of particular OI in that area. Most of the IRIS are short lived or cause minor clinical problems others especially that of central nervous system may result in significant morbidity and even death. Strategies to prevent IRIS will require knowledge about its risk factor and development of the therapeutic approaches will require a better understanding of the pathogenic mechanism.

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