Focus

Immune reconstitution inflammatory syndrome after initiation of highly active anti-retroviral therapy in HIV/AIDS

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INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction in HIV infected patients after initiation of antiretroviral therapy (ART) resulting from restored immunity to specific infectious or non infectious antigens.

In the infectious category, most frequently reported cases are - *Mycobacterium tuberculosis* (TB), cryptococcal meningitis, varicella zoster, herpes viruses, CMV, *Pneumocytis (carinii)* jiroveci pneumonia (PCP), hepatitis B and C etc.[1] Other conditions i.e. *Mycobacterium avium* complex (MAC), latent cryptococcal infection are also reported. The non infectious causes include rheumatoid arthritis and other auto immune diseases.[2] Besides a direct reaction to infectious and non infectious agents, a third group of patients reacts as a result of their host genetic susceptibility. For example, they carry specific HLA alleles like HLA class II, interleukin –1 (IL-1), IL-6, TNF-α develop IRIS to specific antigens.[3]

PATHOGENESIS

The commonest condition where IRIS has been reported is tuberculosis (TB). In some cases, patients starting antituberculosis treatment develop an exacerbation of the symptoms and signs of TB. This occurs more frequently if the patient is HIV positive. The etiology of this reaction is unknown. It is believed that the immune system is reconstituted with sufficient vigor and behaves abnormally in the presence of tubercle antigens produced either by dead or dying bacilli. A similar reconstitution occurs in HIV patients with tuberculosis when highly active anti-retroviral therapy (HAART) is initiated. It is thought that the immune system recovers from profound immune suppression reacting vigorously to dead bacilli killed by HAART, sometimes in the absence of anti-tuberculosis treatment. Therefore, this reaction is often seen after HAART initiation in late stage of HIV disease when immune system is profoundly suppressed with few CD4 cells and high HIV viral load. In late stages of HIV infection, absolute CD4 T cell nadirs of less than 100 cells /μl who receive HAART, respond to treatment with a sudden increase of CD4 cells and undetectable HIV plasma viremia with a robust immune reaction.[4]

British HIV Association guidelines which are strictly followed in UK mention a study (without reference) under the topic of IRIS with a median base line CD4 cell count of 35 cells/uL and a median HIV RNA load of 580,000 copies/ml before commencement of HAART.[5] It is quite possible that lower the CD4 count more severe is the response expected. Although the exact pathogenesis is not known, there may be some other immune mechanism in addition to cellular mechanism. It has been reported that the successful response to treatment with HAART produces pro-inflammatory cytokines or an immune deregulation by absence of regulatory cytokines results in a robust immune system. This activation of the immune system can be measured quantitatively by gut immune components which allow an increased translocation of bacterial liposaccharides (LPS) in to systemic circulation in cases of IRIS.[3]

Therefore, IRIS is a paradoxical adverse immune

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reaction due to pathogen specific immune response during the initial months of HAART.

EPIDEMIOLOGY

Mycobacterium tuberculosis (TB) is among the most frequently reported pathogen associated with IRIS. TB-IRIS is reported to be around 36% in the developed countries where patients were on dual therapy (antiretroviral therapy or ART) in 1990s when HAART was not available.[2] The symptoms in the groups which received ART and TB therapy were severe than in the control group which received only TB therapy.[1] IRIS-TB is also prevalent in the developing countries. It is reported to be between 11 to 43%.[5] In resource limited developing countries like India it was reported to be 8% in 2007.[3] The low prevalence was probably due to non-availability of HAART to HIV patients with TB. The incidence of IRIS is expected to rise in this patient group because of the wide availability of HAART in India now.

On August 12, 2009, US Food and Drug Administration (FDA) approved the generic use of the long awaited daily single tablet of FTC 200mg/efavirenz 600mg/ tenofovir 300mg to be marketed in India, manufactured by Matrix.[6] On September 3, 2009, Matrix was further allowed by FDC to produce a different single tablet containing three anti-retrovirals with 3TC 300mg instead of FTC.

Mycobacterium avium intracellular complex (MAC) was first noticed to cause IRIS when AZT (zidovudine) monotherapy was in use for AIDS in 1992. [7] The sub clinical infection of cytomegalovirus (CMV) usually becomes clinically significant with immune recovery uveitis and immune recovery vitritis after initiation of HAART. This CMV related IRIS was found to be very common i.e.18%.[8] Varicella zoster (herpes zoster) associated IRIS is also very common after initiation of HAART. It is reported to be around 9-40%.[9]

In single cohort of 41 cases of cryptococcal meningitis, 33 cases (80%) were associated with IRIS.[10] IRIS has been reported in leprosy. Previously undetected leprosy has been diagnosed after onset of IRIS in HIV patients.[11,12] Although the prevalence of leprosy is falling in India, its recognition, especially tuberculoid leprosy, and diagnosis is important in the management of IRIS.[13]

CLINICAL FEATURES

The commonest clinical manifestations of TB-IRIS are fever, lymphadenopathy, and respiratory symptoms. New pulmonary infiltrates, mediastinal lymphadenopathy and pleural effusion can be seen. Extra pulmonary manifestations include disseminated TB with acute renal failure and intracranial tuberculoma, non-specific abdominal pain and obstructive jaundice. TB-IRIS is usually seen soon after starting HAART.

In one series of 43 cases, IRIS was seen at a median onset of 12-15 days (range between 2-114 days). In this series only four cases started after four weeks.[2] Therefore doctors should maintain high degree of vigilance during this early period of HAART. In CNS involved TB-IRIS with intracranial tuberculoma, TB meningitis and spinal cord lesions, the symptoms tend to occur late, usually 5-10 months after starting HAART.[13]

In all suspected cases it is important to obtain relevant clinical samples i.e. sputum, pleural fluid, urine, pus, peritoneal fluid, CSF etc for culture of *Mycobacterium tuberculosis* to establish the diagnosis. In HIV positive patients with sufficient immune suppression Mantoux test and Ziehl-Nielson staining of smears may be negative. If a biopsy is carried out, caseating granuloma is the hall mark of TB. A chest X-ray may show consolidation, cavitation, fibrosis and calcification.[14]

In MAC-associated IRIS, the symptoms are more or less like TB-IRIS. The development of MAC-IRIS lymphadenitis is usually after 17 days (range 17-85 days).[15] In CMV retinitis, IRIS is usually seen after four to seven weeks of starting the HAART.[16] The diagnosis of MAI depends on the culture and biopsy of the lymphnodes.[14]

Cryptococcus meningitis is usually suspected when there are symptoms suggesting increased intracranial pressure i.e. headache, confusion, papilloedema and cranial nerve lesions. Cryptococcal organisms can be detected in the CSF by India ink staining and a positive blood culture.[14]

TREATMENT

The treatment of IRIS depends on the severity at

presentation. Appropriate treatment for the specific cause of IRIS, including HAART, should be adequate. However, in life threatening presentations like acute renal failure or acute respiratory distress syndrome (ARDS), systemic corticosteroid in the doses of 1-1.5mg/kg/day along with non-steroidal anti-inflammatory drugs (NSAIDs) should be started without delay. The duration of IRIS treatment is usually for four weeks. The dose of the steroid should be reduced after two weeks. Some authors have argued for longer duration up to 12 weeks.[1] According to British HIV Association (BHIVA) guidelines the use of NSAIDs tend to be not helpful.[5]

The guidelines to start the treatment with HAART depend on the absolute CD4 counts. If CD4 count is less than 100 cells/μl, both anti tuberculosis drugs and HAART can be started together, If CD4 cells are in the range of 100-200, HAART is started two months after starting TB treatment. If the CD4 cells are above 200, HAART is started six months after completing TB treatment. These guidelines are issued by BHIVA.[5]

Rifampicin in the treatment of TB-IRIS induces the metabolism of steroids and effectively reduces the efficacy steroids by 33-50% only after one to two weeks.[5] This does not make any difference to the patient's condition as they would have improved by then. There has been no study on patients who do not improve after two weeks on steroid.

Steroid doses should not exceed beyond 1.5 mg/kg/day. Probably one can think of changing rifampicin to rifabutin. Rifabutin is a potent enzyme inducer of CYP3A4. If given with ritonavir or lopinavir as a part of HAART, the dose of rifabutin should be halved to 150 mg three times a week and if given with efavirenz its dose should be increased to 450 mg but no change with nevirapine. Multi-drug resistant TB (MDR-TB) where *M. tuberculosis* is resistant to both rifampicin and INH requires close follow-up and the treatment should be individualized based on resistance with at least four effective drugs.

Extensive drug resistant TB (XDR-TB) was first reported in 2006 in USA and is common in HIV patients. In case of MDR-TB and in XDR-TB special advice should be sought from experienced doctors. In case of cryptococcal meningitis induced-IRIS, antifungal treatment is given in three phases; the induction phase for 14 days with amphotericin B, the consolidation phase with fluconazole for eight weeks and finally suppressive phase with maintenance dose of fluconazole.[17] During induction phase, amphotericin B is given IV in the doses of 0.7mg/kg/day and 5 fluorouracil given orally 100mg/kg/day. After 14 days in the consolidation phase, fluconazole is given orally 400 mg /day for eight weeks. It is expected that in eight weeks of fluconazole therapy, the CSF would be sterile, if not the treatment is continued until the CSF is sterile after which maintenance therapy starts with 200mg of fluconazole/day for life. It is possible that during lumbar puncture (LP) the intracranial pressure may be elevated. If the opening pressure is less than 250 mm H_2O, there is no need to take any action to reduce the pressure further. If it is more than 250 mm it should be reduced to 200mm or if it is too high it should be reduced to half of the opening pressure, by CSF drainage. This low pressure should be maintained even with daily LP.

CONCLUSION

IRIS is an inflammatory reaction found among HIV-positive patients when antiretroviral treatment is started. The etiology is unknown but it is thought to be a reactivation of suppressed immune system after profound suppression by the HIV. The sudden increase of CD4 cells after immune reactivation by highly active antiretroviral therapy (HAART) are involved with the antigens of dead HIV. IRIS is also seen among patients with TB without HIV. When HIV is present with confection of TB, the reaction is severe. IRIS has also been reported in other confections i.e. MAC, herpes zoster, CMV and cryptococcal meningitis. However, *M. tuberculosis* is the most frequently reported pathogen. In most cases the treatment for HIV with HAART is sufficient. The co-infection should be treated appropriately. No special or additional treatment for IRIS is required. However, in life threatening conditions with acute renal failure or acute respiratory distress treatment with steroids should be started without delay.

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