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Repuestas paradójicas en pacientes bajo terapia antirretroviral (Immune Restoration Syndrome of HAART)

Gordon Dickinson, M.D. – Universidad de Miami, EE.UU.

The first successful trials with zidovudine, conducted at a time (1985-86) when quantitative assays of HIV were not available, demonstrated that an effective antiviral agent improves both laboratory and clinical manifestations of cellular immunity. T-helper lymphocyte numbers increased and the risk for opportunistic infections decreased. We now know that this restoration also may establish a brisk host response to latent, incipient and partially treated opportunistic infections. These inflammatory reactions, paradoxical in the sense that they occur in the patient responding to HAART, has been termed the "immune restoration syndrome". This syndrome - or syndromes – can be organ or life threatening, may be very difficult to distinguish from an adverse drug reaction, and a challenge to manage. A listing of opportunistic pathogens and infections reported in association with the IRS are shown in the table below; other pathogens – for example, leishmaniasis, toxoplasmosis – are likely to be linked to this syndrome as well.

Opportunistic Infections Associated with an Immune Restoration Syndrome following initiation of HAART

Cytomegalovirus
Cryptococcus neoformans
Hepatitis B
Hepatitis C
Herpes zoster
Histoplasma capsulatum
Mycobacterium avium complex
Mycobacterium tuberculosis
Progressive multifocal leukoencephalopathy

The syndrome is usually seen in the severely immunosuppressed individual within weeks of initiation of HAART. The manifestations are related to the specific opportunistic infection. For example, the patient with CMV retinitis may develop loss of vision and have evidence of retinal inflammation, whereas the patient with chronic active Hepatitis B will experience a dramatic rise in transaminases and, perhaps, right upper quadrant tenderness, nausea, etc. Pulmonary TB responding to therapy may suddenly seem to relapse with fever, cough and increasing infiltrates on the chest X-ray. It has been observed, however, that these reactions do not mimic the usual clinical presentation of the underlying opportunistic infection. For example, the patient with CMV retinitis often has uveitis with the IRS, an unusual manifestation of typical CMV retitinitis. Disseminated Mycobacterium avium complex infection is usually indolent in onset with

generalized symptoms whereas the IRS of MAC often presents as localized lymphadenitis. In general, the IRS presents more abruptly than the corresponding opportunistic infection.

The IRS is not related to progression of the underlying infection – cultures are usually negative in infections where the cultures might be expected to be positive if the clinical picture was due to progression of the infection. The pathogenesis, not yet well defined, is attributed to the improved host response to residual antigenic material still present at the site of the infection. The IRS is analagous to similar syndromes reported with leprosy, TB and in patients discontinuing immunosuppressive treatment.

In general, the continuation of therapy with symptomatic treatment and monitoring the patient will be sufficient and the IRS will subside in several weeks time. In some cases, however, the syndrome may be life-threatening. For example, TB meningitis may be associated with such an intense reaction that it causes cerebral edema or spinal ischemia as the inflammatory reaction compromises the blood vessels. In this situation, suppression of the IRS with corticosteroids may be required.

The management options include symptomatic treatment, delaying HAART until the treatment of the OI has eliminated the residual antigenic material thought to contribute to the IRS, or to continue HAART and suppress the IRS with corticosteroids.

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