Paradoxical response in tuberculosis and reversal reaction in leprosy. *Different terminology for same immunology?*

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It is well known that paradoxical response (PR) in tuberculosis (TB) leads to a temporary "flare up" of the disease. In the first 3-12 weeks after initiation of an apparently adequate regimen, old lesions may enlarge or few lesions may develop. It has many manifestations, the most frequent being an increase in the size of tubercular lymphadenopathy (30%), and increase in the size of brain or spinal tuberculomas (16%). Other manifestations include increase in the size of pleural effusion on the same side or appearance of pleural effusion on the other side, and occasionally a respiratory distress syndrome-like presentation.[1] Appearance of new lymphadenopathy while treating TB of the nervous system has also been documented.[2] When TB is not involving a specific organ, like in miliary TB, PR may manifest as continuation or emergence of fever. This is however accompanied by other parameters of positive response to anti-TB therapy.

In leprosy especially borderline, borderline tubercular (BT) and borderline lepromatous (BL) a similar phenomenon is seen when patient is started on treatment. It may even be seen when the nutritional status of these patients improves. These patients move towards the tuberculoid pole of leprosy and manifest with swelling, erythema and scaling of the existing skin lesions or appearance of new skin lesions. The hands and feet and sometimes the face may become edematous. These reversal reactions (RR) usually commence within a few weeks of the start of treatment in BT, but often only after several months of treatment in BL and lepromatous leprosy (LL) although lepromin test may become positive after around 20 years of treatment.[3] Functional nerve damage may also occur in already enlarged nerves. Inactive TB, the delayed type hypersensitivity (DTH) response is depressed. Once effective treatment is started and acid fast bacilli (AFB) are killed, TB is under control, lymphocytes start aggregating at site of TB involvement. This leads to PR.

Similar mechanism has been noted in leprosy. From lymphocyte transformation studies, RR is thought to be due to an increase in DTH, usually associated with an increase in cell-mediated immunity. Such reactions may be produced experimentally by the administration of syngeneic lymphocytes in thymectomised-irradiated or nude mice that have already developed lepromatous leprosy.[4] More recently patients with acquired immunodeficiency syndrome who were treated for TB developed PR, which has been given the generic name of 'reactivation syndrome'(RS) or 'immune reconstitution syndrome'. Reactivation syndrome usually occurs in first 4 weeks (15 ± 11 days) after initiation of antiretroviral treatment. Navas et al[5] confirmed that PR are more likely to occur in patients with larger reductions in viral load and higher increases in cluster of differentiation 4 + cell count. In fact, PR was only seen in patients receiving highly active antiretroviral therapy (HAART) regimen. This syndrome was attributed to the immunologic recovery produced by HAART, which could enhance the inflammatory response around the infection, producing a relapse of clinical symptoms. Immune reactivation mechanism may also account for other paradoxical responses such as focal lymphadenitis due to Mycobacterium avium-intracellulare seen after institution of effective antiretroviral therapy.[6]

Both TB and leprosy are chronic granulomatous disease and does AFB produce both. PR, RR and RS are temporary phenomenon and severe reactions are treated with oral corticosteroids (RR may require treatment for months). However controversy surrounds the phenomenon. Return to DTH has been challenged. Are only chronic granulomatous diseases incriminated as causes? Or is it specific to AFB cell wall component lipoarabinomannan which may cause monocytes to release TNF-alpha eliciting a systemic immune response?[6] Is different terminology being used in different diseases for the same immunologic manifestations? These issues are yet to be resolved.

Clinical awareness regarding PR, RR as well as RS is of paramount importance in avoiding misdiagnosis or mismanagement. Recognition of this rare occurrence is important, due to lesions regress without change in the initial regimen.

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