To have not and then to have: A challenging immune paradox

Clinicians are well aware of the increased risk of infection in immunosuppressed patients. But the ecologic balance between infectious agents and the immune system is complex. All immunosuppression is not equal, and the complexity relates to more than just the degree of depressed immunity: the affected arm of the immune response matters. Patients with neutropenia are prone to different infections than patients with T-cell disorders or hypogammaglobulinemia. Similarly, the character of the inflammatory response (eg, pyogenic, granulomatous, fibrotic) depends on the interaction between the infectious trigger and the specific activated arm of the immune response. This interaction dictates how the native tissue may be transiently or permanently affected.

The successful interplay between the host defense system and infectious invaders depends on controlling the tissue damage that ensues from both the infection and the resultant inflammatory response. Even though an underactive immune system predisposes to unusual and potentially severe infections, an overly vigorous host response to infection can be as destructive as the infection itself. We can improve the outcome of some infections by introducing potent anti-inflammatory and immunosuppressive therapy concurrent with appropriate anti-infective therapy. What initially seemed counterintuitive has become the standard of care in the treatment of bacterial and mycobacterial meningitis and severe *Pneumocystis* and bacterial pneumonias, and favorable data are accruing in other infections such as bacterial arthritis.

A twist on the above scenario can occur when an immunosuppressed patient with a partially controlled indolent infection has his or her immune system suddenly normalized due to successful treatment of the underlying cause of their immunodeficiency. This treatment may be the introduction of successful antiretroviral therapy against human immunodeficiency virus (HIV), effective therapy of an immunosuppressing infection like tuberculosis, or withdrawal of an immunosuppressive anti-tumor necrosis factor (anti-TNF) drug. In this scenario, where the immune system is rapidly reconstituted and concurrently activated by the presence of persistent antigenic challenge or immunostimulatory molecules, a vigorous and clinically counterproductive inflammatory response may ensue, causing "collateral damage" to normal tissue. This immune reactivation syndrome may include fever, sweats, adenitis, and local tissue destruction at the site of infectious agents and associated phlogistic breakdown products. The result of this robust, tissue-injurious inflammatory response can be particularly devastating if it occurs in the brain or the retina, and may cause diagnostic confusion.

The trigger for this regional and systemic inflammatory response is multifactorial. It includes the newly recovered responsiveness to high levels of circulating cytokines, reaction to immune-stimulating fatty acids and other molecules released from dying mycobacteria (perhaps akin to the Jarisch-Herxheimer reaction to rapidly dying spiro-

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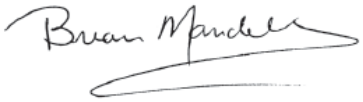
chetes), and possibly an over-vigorous "rebooting" immune system if an appropriate regulatory cell network is yet to be reconstituted.

In this issue of the *Journal*, Hara et al (page 914) provide images from a patient appropriately treated for tuberculosis who experienced continued systemic symptoms of infection with the appearance of new pulmonary lesions. The trigger was the withdrawal of the infliximab (anti-TNF) therapy he was taking for ulcerative colitis, which at face value might be expected to facilitate the successful treatment of his tuberculosis. This seemingly paradoxical reaction has been well described with the successful treatment of HIV-infected patients coinfected with mycobacteria (tuberculous or nontuberculous), cytomegalovirus, and herpes-associated Kaposi sarcoma and zoster. But as in this instructive description of a patient with an immune reactivation syndrome, it also occurs in the setting of non-HIV reversibly immunosuppressed patients.[1,2] The syndrome is often recognized 1 to 2 months after immune reconstitution and the initiation of anti-infective therapy.

The treatment of this paradoxical reaction is (not so paradoxically) the administration of corticosteroids or other immunosuppressive drugs. The efficacy of corticosteroids has been demonstrated in a small placebo-controlled trial[3] as well as in clinical practice. The mechanism driving this reaction may not be the same for all infections, and thus steroids may not be ideal treatment for all patients. There are reports of using infliximab to temper the immune reactivation syndrome in some patients who did not respond to corticosteroids.

There is no definitive confirmatory test for immune reactivation syndrome. And certainly in the case of known mycobacterial infection, we must ensure the absence of drug resistance and that the appropriate antibiotics are being used, and that no additional infection is present and untreated by the antimycobacterial therapy. While lymphocytosis and an overly robust tuberculin skin test response have been described in patients with tuberculosis experiencing an immune reactivation syndrome, this "paradoxical reaction" remains a clinical diagnosis, worth considering in the appropriate setting.



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