References


Paradoxical Reaction during Tuberculosis Treatment in HIV-Seronegative Patients

Sir—We read with interest the article by Hawkey et al. [1] describing the occurrence of paradoxical reaction (PR) during antituberculous treatment among HIV-seronegative patients with lymph node tuberculosis (TB). In another recent issue of Clinical Infectious Diseases, Vidal et al. [2] described 4 patients who developed TB after treatment with infliximab and in whom the site of PR was mainly the lymph nodes. In our experience, among HIV-seronegative patients with TB, the CNS is a more frequent site of PR than the lymph nodes. The importance of the CNS as a site of PR has been recognized in previous reports [3, 4].

From January 2003 to December 2004, at the outpatient TB clinic of the University of Brescia (Brescia, Italy), we studied the frequency of cases of TB with PR, as well as the clinical characteristics of HIV-seronegative patients with TB who had PRs. PR was defined as a clinical or radiological worsening of previous TB lesions or development of new lesions after at least 1 month of TB treatment in a patient who initially responded to antituberculous therapy (figure 1). PR was detected in 11 (8%) of 137 HIV-seronegative patients with TB. Eight patients (73%) were men, 10 (90%) were immigrants, the median age was 37 years (range, 26–68 years), 4 (36%) had isolated extrapulmonary TB (3 had lymph node TB and 1 had spinal TB), and 7 (64%) had disseminated TB. The median time to PR onset was 107 days (range, 31–443 days). Infection of cerebral tuberculosis (6 patients [50%]) and lymph node enlargement (5 patients [42%]) were the main manifestations of PR. Nine (82%) of 11 patients had an initial positive culture result for Mycobacterium tuberculosis, which was sensitive to all first-line TB drugs. At the moment of PR occurrence, new bacteriological tests were performed for 6 patients (54%), and needle aspiration was performed for all 5 patients with lymph node enlargement. These test results were negative for M. tuberculosis for all but 1 patient, a woman from Pakistan who had a strain of M. tuberculosis with the same pattern of sensitivity as the initial isolate from the inguinal lymph node. PR was significantly associated with disseminated and extrapulmonary TB (29% and 11% of patients, respectively, had PR, compared with 0% of patients with pulmonary TB who had PR; P = .002), but no association between PR and sex, age, or ethnicity was found. TB therapy was changed for 2 patients (18%) with cerebral tuberculosis; pyrazinamide was reintroduced for both patients, and levofloxacin was added for 1 of them. Patients with CNS tuberculosis had antituberculous therapy extended for a median duration of 522 days (range, 315–772 days). Steroid therapy was used to control edema in 4 patients (36%) with cerebral tuberculosis.

PR was not uncommon among HIV-seronegative patients at our TB clinic, and it was significantly more frequent among patients with extrapulmonary or disseminated TB. To distinguish PR from TB treatment failure may represent a clinical dilemma. The initial isolation of drug-sensitive M. tuberculosis and the favorable clinical response to TB treatment experienced by the majority of our patients allowed us to wait for culture results before deciding whether to change antitubercular therapy. Steroid therapy was an important tool for controlling cerebral edema, and the need for and benefit of extended antituberculous therapy remained questionable. Repeated needle aspiration of lymph nodes was implemented to prevent fistula formation and to avoid the need for symptomatic steroid therapy or surgical excision. The bacillary load, but more likely the hypersensitivity response to mycobacterial antigens, seems to be the basis of PR pathogenesis; this has been described in studies of HIV-seropositive patients with TB after introduction of antiretroviral therapy [4, 5]. Disseminated TB and associated conditions, such as HIV infection or infliximab treatment, could represent risk factors for PR, because such conditions allow a large load of bacilli in granulomatous lesions. However, further
Figure 1.  Top, A normal cranial CT scan of a 26-year-old man with an initial diagnosis of pulmonary tuberculosis and tuberculous meningitis. Bottom, CT scan showing an insurgence of cerebral tuberculomas with surrounding edema after 4 months of antituberculous therapy. The same patient also developed cervical lymph node enlargement in the 12th month of antituberculous therapy.
studies are necessary to understand the immunopathogenesis of PR; such studies should help clinicians identify patients who are at higher risk for paradoxical deterioration during TB treatment and better control its clinical manifestations.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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References


Glucose Homeostasis Abnormalities and Gatifloxacin

Str—We read with interest the recent publication by Frothingham [1] reviewing spontaneous adverse event reports (AERs) on gatifloxacin-associated hypoglycemia or hyperglycemia received by the US Food and Drug Administration. Frothingham’s review indicated a clear signal of a higher rate of reports of glucose homeostasis abnormality for gatifloxacin, compared with ciprofloxacin, levofloxacin and moxifloxacin. Our own review [2] of the spontaneous AERs received by the Canadian Adverse Drug Reaction Monitoring Program reported findings that paralleled those made by Frothingham. The Canadian Adverse Drug Reaction Monitoring Program tracks reports of hypoglycemia or hyperglycemia in a category called “Metabolic and Nutritional Disorders.” We found that 93% of all spontaneous AERs in this category for gatifloxacin involved either hypoglycemia or hyperglycemia. Conversely, only 11% of reports for levofloxacin and 10% of reports for moxifloxacin in this category involved either hypoglycemia or hyperglycemia. Analysis of our data indicated that there were significantly more reports of hypoglycemia (P<.0001) associated with gatifloxacin treatment than with either levofloxacin or moxifloxacin treatment. Similarly, the total number of reports involving glucose homeostasis abnormalities (either hypoglycemia or hyperglycemia) were significantly higher for gatifloxacin (P<.0001). The signal was even more striking when we observed that the number of retail prescriptions for gatifloxacin in Canada during the period of analysis was approximately one-tenth of the number of levofloxacin retail prescriptions and one-third of the number of moxifloxacin retail prescriptions [3]. Although we acknowledge the limitations of spontaneous AERs, we would like to highlight the importance of AER surveillance in detecting adverse events that occur rarely (i.e., in <1% of patients) [1].

Acknowledgments

Potential conflicts of interest. The authors have received funding, research sponsorship, and contract work from Bayer, Bristol-Myers Squibb Canada, and Janssen-Ortho; however, this letter and the referenced articles published by these authors were not sponsored by, endorsed by, reviewed by, or made available in advance of publication to any of these companies.

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Clinical Infectious Diseases 2006;42:895
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