Letter to the Editor

Histoplasma capsulatum Serology

I would like to present comments on the paper “Evaluation of Cross-Reactions in Histoplasma capsulatum Serologic Tests” by Wheat et al., which appeared in the March 1986 issue of the Journal of Clinical Microbiology (3). The information presented, particularly if one reads only the abstract, is misleading. Although I disagree with several aspects of the presentation, I will confine my remarks to two issues with which I have the most laboratory and clinical experience. These are cross-reactions with H. capsulatum antigens in the histoplasmosis complement fixation (CF) test and the immunodiffusion test with sera from patients with tuberculosis.

In the Materials and Methods section, it is stated “. . . results of 1:8 or greater were considered positive, as has been recommended by others (22).” Reference 22 was to a 1971 paper by Dr. Leo Kaufman. His interpretation of the CF test for histoplasmosis has been reviewed more recently, particularly in the Manual of Clinical Immunology, 2nd edition (2). (The third edition has the same statement.) In that paper, Dr. Kaufman states a titer of 1:8 was “presumptive evidence of infection with Histoplasma capsulatum.” Nowhere does he state or imply that a 1:8 titer is evidence of infection with this organism. In fact, he goes on to say “titers above 1:32 or rising titers offer strong presumptive evidence of histoplasmosis” and “nonetheless, one cannot rely solely on CF titers above 1:32 as a means of diagnosis since false-positive reactions of that magnitude may occur in patients with other diseases.” Fifty-five specimens in the paper by Wheat et al. had a 1:8 titer in the yeast-form CF test (Fig. 1 in reference 3) and were designated as false-positive. These titers may not be false-positive reactions but may represent antibody from old H. capsulatum infections. Careful interpretation of serologic data, along with other laboratory tests and clinical findings, is essential to arrive at a diagnosis of mycotic diseases.

My second concern is their statement, with respect to cross-reactions, that “5 of 46 patients (11%) with tuberculosis had M precipitin bands by the Histoplasma immunodiffusion test.” In the Materials and Methods section, they state that 21 of the 46 serum samples from patients with tuberculosis came from the Indiana University Medical Center Hospitals. Some of the remaining 25 samples were obtained from Northwestern Medical Center in Chicago, and others were from the National Jewish Hospital in Denver. It is more likely that these M bands indicate past infection with H. capsulatum rather than cross-reaction. I base this statement on two factors: (i) both Illinois and Indiana are areas of high endemicity for histoplasmosis, and (ii) a study of histoplasmosis serology in 300 patients with infection caused by Mycobacterium tuberculosis in a nonendemic area revealed only one positive. This latter study (1) found only one M precipitin in 295 tuberculosis patients tested (0.3%). Four patients were not tested by the immunodiffusion method. It is my opinion that the patients with M precipitins, in both studies, reflected past experiences with H. capsulatum and not cross-reactions.

Many hospital laboratory directors with the responsibility to utilize fungal serology and to select the most appropriate test may be led to wrong decisions based on data of the type presented in the paper under contention.

LITERATURE CITED

Author’s Reply

Dr. DiSalvo quotes Dr. Kaufman in noting that “one cannot rely solely on CF titers above 1:32 as a means of diagnosis since false-positive reactions of that magnitude may occur in patients with other diseases.” Dr. DiSalvo states that “careful interpretation of serologic data, along with other laboratory tests and clinical findings, is essential to arrive at a diagnosis of mycotic diseases.” I entirely agree with those two statements. While, in my experience, serologic tests have proven very valuable in diagnosing histoplasmosis, I fully recognize the limitations of these tests. I stated in the closing paragraph of the earlier article that “until more specific tests become available, careful clinical judgment and additional laboratory examination should be used in assessing the significance of positive serologic tests in individuals with epidemiologic, clinical, and roentgenographic findings which are not highly suggestive of histoplasmosis, especially if the serologic tests are only weakly positive.”

Dr. DiSalvo also notes that M precipitins in patients with tuberculosis are more likely to be caused by past or concurrent infections with Histoplasma capsulatum than by cross-reactions. The immunodiffusion test is more specific than the other serologic tests used in histoplasmosis. I concur that M precipitin bands are more likely to be caused by concurrent or past infections with H. capsulatum than by cross-reactivity with mycobacterial antigens. In the earlier study, I noted the difficulty in assessing the significance of positive serologic tests for histoplasmosis in patients with tuberculosis.

The primary objective of our report was to illustrate the potential for cross-reactivity in serologic tests for histoplasmosis. The implications of these findings are that, first, physicians should use careful clinical judgment in determining the significance of positive serologic tests and, second, more specific serologic tests are needed.

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