Coccidioidomycosis

STUDY GROUP

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Abstract 1: Summary of Prospective Study on Coccidioidomycosis in Subjects with HIV Infection Living in Coccidioidal area

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We have been studying the incidence of active coccidioidomycosis in HIV-infected subjects living in the coccidioidal endemic area for over the past 2 years. As of March, 1991, 170 subjects have entered the study and have been followed for a median of 5.2 months (range 0 - 27.3 months). 85.3% of the subjects were white, 96.5% were male, and 89.4% had HIV risk factors of either gay life style or intravenous drug abuse. The mean ± SEM age was 38 ±1 years and the mean ± SEM time in the endemic area was 131 ± 10 months. Thirty-eight subjects (24.4%) demonstrated dermal hypersensitivity to spherulin on entry to the study. Spherulin skin-test positivity was significantly associated with a CD4 lymphocyte count >= 200/uL (p 0.0118). To date, 8 subjects have developed active coccidioidomycosis during follow-up. All were white males and had lived in the endemic area from 25 to 506 months. Only one had a prior history of coccidioidomycosis. At the time of the development of active coccidioidomycosis, all but one had CD4 lymphocyte counts <200/uL. Three had positive spherulin skin tests at that time of diagnosis, two of these subjects were previously skin-test positive. Four of the subjects are still alive. The three who died had diffuse pulmonary disease. Using the method of Kaplan and Meier, the incidence of active coccidioidomycosis can be estimated as 13.1 % over 20 months (95% confidence limits: 3.7 - 22.5%). A CD4 lymphocyte count of < 200/uL was the only factor clearly associated with the development of active coccidioidomycosis, with an odds ratio of 24.6 (95% confidence limits: 1.0 - 576.1). Factors not associated with the development of active coccidioidomycosis include a positive spherulin skin-test and living in the endemic area for > 25 months. These results indicate that active coccidioidomycosis among the HIV infected is not uncommon in the coccidioidal endemic area. Impaired cellular immune function, as manifested by a low CD4 lymphocyte count, is the only factor associated with active coccidioidomycosis..

Abstract 2: Coccidioidomycosis and Pregnancy

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The course of coccidioidomycosis (coccy) in relation to pregnancy was reviewed from cases presented in the literature and from unpublished cases coming to our attention through our coccidioidal serodiagnostic activities. From the literature 18 patients had coccidioidomycosis prior to pregnancy. Nine of these 18 had disseminated coccy, one of whom exacerbated her disease during pregnancy, and 1 patient died with disseminated coccy. (Two others died after the completion of pregnancy.) One of the 18 had a pulmonary cavity which remained unaffected by the pregnancy. Sixteen patients acquired primary coccy during the first trimester, 6 of the 16 (37.5%) developed disseminated disease, and three of the 16 (18.75%) died. Twelve acquired coccy in the second trimester, 6 of these (50%) underwent dissemination and 5 (41.7%) died. Twenty-six acquired coccy in the third trimester, 19 disseminated, and 15 (57.7%) died. Of the unpublished, 16 cases had coccidioidomycosis prior to pregnancy. Eight with pulmonary cavities remained stable. Five had disseminated coccy. One of these 5 relapsed during pregnancy but none died. Seven acquired coccy in the first trimester, one of these (14%) disseminated, none died. Five acquired coccy in the second trimester, 4 disseminated (80%), and 1 (20%) died. In the third trimester, 12 acquired primary coccy, 7 (58%) disseminated and 3 (25%) died. Of the confirmed published and unpublished cases rates of dissemination and fatality respectively were 22.7% and 13.6% for the first trimester, 58.8% and 35% for the second trimester, and 68.4% and 47% for the third trimester. Therefore, there is an increasingly high risk of dissemination the later in pregnancy primary coccy occurs.

Abstract 3: The Formation and Regeneration of Protoplasts of *Coccidioides immitis*

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Endospores and immature spherules from synchronously growing cultures and mycelia were used in a series of experiments to produce protoplasts. It was determined that newly-released endospores could be readily converted to protoplasts with greater than 99% efficiency with a one hour treatment with snail-gut enzyme and a chitinase derived from *Serratia marcescens*. Immature spherules were more resistant to this approach, but could be converted with approximately 90% efficiency after two hours of treatment if an endochitinase derived from corn meal was added to the enzyme mixture. Mycelia were more resistant, with an approximate 40% conversion to protoplasts after two hours of enzymatic digestion in the latter mixture. All attenpts to regenerate the cell wall of the protoplasts failed, possibly due to contamination of the endochitinase preparation by EDTA.

Abstract 4: Isolation of an Immunologically Active 33kDa Cell Wall Apoglycoprotein from *Coccidioides immitis*

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Antigens released from mature spherules of *C. immitis* by exposure to 3% toluene were deglycosylated with anhydrous HF to yield an A_{280} peak following gel filtration chromatography or RPHPLC with an apparent M_r of 33 KDa on silver stained SDS-PAGE gels. This antigen did not show identity with the diagnostic antigens CF, TP, or HS. However, tandem 2-dimensional immunoelectrophoresis showed anodal fusion of the purified antigen with reference antigen 2. Amino acid analysis showed the 33 KDa antigen to be rich in proline (17.9%) and threonine (14%). In immunoblots, sera from *C. immitis*-infected patients but not from controls reacted strongly with the purified 33 KDa protein. Antibodies from patient sera were affinity purified, used in immunoelectron microscopic studies, and detected the protein in the walls of spherules, endospores, and arthroconidia. Peripheral blood mononuclear leukocytes from 5 subjects with dermal hypersensitivity to spherule-derived antigens reacted significantly more to the antigen than did cells from 5 subjects with nonreactive skin tests (mean±sem cpm: 5,656±1,579 versus 636±268, $p < 0.01$. It is possible that the protine is important in human immune recognition of coccidoidal infection.

Abstract 5: Coccidioidomycosis During HIV Infection; Results of Prospective Study in a Coccidioidal Endemic Area

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Abstract:
PURPOSE: To determine the incidence of active coccidioidomycosis among subjects infected with the human immunodeficiency virus (HIV) living in an area endemic for coccidioidomycosis and to identify factors associated with the development of active coccidioidomycosis in these patients. PATIENTS AND METHODS: This was a prospective cohort analysis of HIV-infected subjects living in an area endemic for coccidioidomycosis in Arizona. On entry and at approximately 4-month intervals, subjects were interviewed and examined, and had spherulin skin testing and CD4 lymphocyte counts performed along with other tests. During each interval, it was determined whether the subject had developed active coccidioidomycosis according to established criteria. RESULTS: One hundred seventy subjects entered the study. Median follow-up was 11.3 months (range: 0 to 44 months). Thirteen subjects developed active coccidioidomycosis, with an estimated cumulative incidence of 24.6% by 41 months (95% confidence limits 8.2% and 41.1%). Risk factors associated with the development of active coccidioidomycosis in the cohort were a CD4 lymphocyte count of less than 0.250 x 10(9)/L and a diagnosis of acquired immunodeficiency syndrome. Factors associated with prior coccidioidal infection, including a positive spherulin skin test, length of residence in the endemic area for more than 25 months, and a prior history of coccidioidomycosis, were not associated with the development of active infection. CONCLUSION: Active coccidioidomycosis among individuals infected with HIV is common in the coccidioidal endemic area. Immunodeficiency appears to be the major risk factor for the development of disease. Evidence of prior coccidioidomycosis, including a positive spherulin skin test, does not appear to predict the development of active infection.

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