8.7.3 Coccidioidomycosis 1361

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8.7.3 Coccidioidomycosis 1361 treatment. An approach similar to that recommended for immuno-suppressed patients is still recommended, such as an initial (2–4 weeks) of amphotericin B-based induction therapy followed by 8–10 weeks of fluconazole. More prolonged use (4–6 weeks) of amphotericin B and flucytosine might be more rapidly curative but is also more toxic. Cryptococcal meningitis in AIDS requires lifelong suppressive therapy unless the immunosuppression is reversed with effective treatment of HIV infection. In that circumstance, treatment can be discontinued if the CD4+ lymphocyte count increases to over 200 cells/mm3. In other immunocompromised patients, suppressive treatment for 6 to 12 months can be given. Effective antiretroviral therapy might also sufficiently improve the immune system such that there is an immunological response to the fungal infection. This might be associated with clinical deterioration and apparent relapse of symptoms; this immune reconstitution inflammatory syndrome (IRIS) should not prompt change in antifungal therapy and patients should receive anti-inflammatory therapy, as needed. It has also been described in transplant patients whose immunosuppressive therapy is decreased during management of the cryptococcal infection. Timing of initiation of antiretroviral therapy in HIV-infected pa- tients is a very important consideration. Recent randomized clinical trials suggest that early (within two weeks of diagnosis) initiation of antiretroviral therapy is associated with an increased mortality in patients with cryptococcal meningitis, possibly because of the devel- opment of immune reconstitution syndrome. This means that there is often a delay in starting antiretrovirals for a few weeks to avoid this complication. However, recent studies suggest that screening for CrAg, with preemptive fluconazole for those infected, before starting antiretrovirals reduces IRIS and mortality. Fluconazole, 200 mg daily, is the suppressive treatment of choice. Fluconazole, in dosages ranging from 400 mg weekly to 200 mg daily, and itraconazole, 100 mg twice daily, are very effective in preventing invasive cryptococcal infections, especially in HIV-positive patients with CD4 counts less than 50–100 cells/mm3. However, because of the relative infrequency of invasive fungal infections, antifungal prophylaxis does not prolong life and is not routinely recommended where antiretroviral therapy is readily available. An approach using CrAg screening and pre-emptive antifungal therapy in ART-naive individuals with a CD4 count of less than 100 cells/mm3 is currently being evaluated in high incidence settings. FURTHER READING

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 isolates). Both species produce similar clinical effects. These soil fungi inhabit semiarid to arid areas in the south-western United States of America and parts of Latin America. Hyperendemic areas include the San Joaquin Valley (California) and Pima, Pinal, and Maricopa counties in Arizona. There are approximately 150 000 infections per year in the United States of America, and about one-third of those infected become symptomatic. Persons at risk Residence in or travel to endemic areas is the key risk factor for ac- quiring coccidioidomycosis. Arizona accounts for about 60% of re- ported American cases. At increased risk of more serious disease are people of Filipino or African American descent, those with blood group B, those exposed to soil, and the immunocompromised (organ transplant recipients; HIV infection, cancer,

and diabetes; pregnancy; recipients of tumour necrosis factor α antagonists). Outbreaks may follow dust storms, earthquakes, droughts, and ac- tivities causing soil disruption, such as archaeological digs. Recent data from Arizona have defined a primary exposure season with peaks in May and September, which correlates with seasonal rainfall. Pathogenesis Inhaled coccidioides arthroconidia are ingested by pulmonary macrophages and, over 3 days or more, convert to thick-walled round spherules containing hundreds of endospores. When spher- ules rupture, the endospores may disseminate to meninges, bones, skin, or other soft tissues. Resolution of coccidioidomycosis de- pends on intact cell-mediated immunity. Diagnosis This is based on clinical findings supported by microbiological, histopathological, and/or serological evidence. Coccidioides mycelia grow readily on many culture media. They are formed by barrel- shaped arthroconidia, with intercalated 'ghost' cells. The mycelia are extremely fragile, and the minimum infective dose approaches one arthroconidium, so these fungi must be handled with great caution by laboratory personnel. Coccidioides is considered a potential agent for bioterrorism, and there are strict rules for its handling in the United States. Histopathological findings can vary, from abscesses with many spherules, large endospores, and neutrophils (in uncon- trolled disease) to well-formed granulomas with few organisms (in patients with competent cell-mediated immunity). These findings are readily seen with haematoxylin and eosin staining. Serological methods are often used for the diagnosis of coccidi- oidomycosis. IgM antibodies, detected by the tube precipitin (TP) test or immunodiffusion TP, appear within the first few weeks of in- fection and clear within 1 or 2 months. IgG is detectable by comple- ment fixation (CF) or immunodiffusion CF after several months and persists for years. Serum CF titres of 1:16 or higher suggest deterior- ation or dissemination. In coccidioidal meningitis, any positive titre confirms the diagnosis; the cerebrospinal fluid IgG titre is positive more than 75% of the time, whereas cerebrospinal fluid cultures are positive in less than 50% of patients. More recently, enzyme-linked immunosorbent assay (ELISA) has been used for coccidioidal IgG and IgM antibodies. ELISA optical density correlates roughly with immunodiffusion CF titre. Negative ELISA results do not require confirmation by other tests. However, positive tests may not be entirely specific, and should be confirmed by immunodiffusion or complement fixation tests. A diagnostic test based on the detection of coccidioidal antigens in the serum and urine has been commercialized by Miravista Laboratories. However, problems with this test include low sensitivity and cross-reaction with histoplasma and blastomyces antigens. Clinical presentation Primary infection About 60% of subjects are asymptomatic. Symptomatic primary infec- tion presents from 1 to 3 weeks after exposure, with fever, cough, and pulmonary infiltrates, and may be accompanied by hypersensitivity manifestations, such as erythema nodosum, erythema multiforme, and arthritis. Eosinophilia or eosinophilic pleocytosis (in meningitis) may be present. Usually, however, the clinical syndrome of primary coccidioidal pneumonia is similar to other forms of community-acquired pneu- monia, and this contributes to the difficulty of making a specific diag- nosis. In high-incidence areas, such as Pima or Maricopa Counties in Arizona, coccidioides is the cause of up to 29% of community-acquired pneumonia. It is now recommended that patients presenting with community-acquired pneumonia in highly endemic areas should be tested for coccidioidomycosis. Although antifungal therapy is not re- quired for the treatment of primary infection, it is now understood that primary coccidioidal pneumonia can be an infection with significant morbidity, resulting in prolonged respiratory symptoms and delays in return to normal activity levels. Treatment of primary disease should be undertaken with immunocompromised patients. Recent appreciation of the clinical significance of primary coccidioidomycosis makes up a substantial percentage of community-acquired pneumonias in Arizona again raises the question whether fluconazole should be used more rou- tinely for primary disease. In addition to uneventful

resolution, there are various outcomes of primary coccidioidomycosis, which include those given below. Coccidioma formation Pulmonary infiltrates may contract into an asymptomatic mass (coccidioma), which can persist for years. In an immunocompetent person, antifungal therapy is unnecessary. Progressive/persistent pneumonia Heavily exposed immunosuppressed patients may develop acute respiratory failure. Amphotericin B treatment is recommended. Pneumonia persists more than 2 months, with extensive infiltrates and, often, cavitation. Initial treatment with amphotericin B is re- commended if the patient is severely ill. The Infectious Disease Society of America guidelines suggest between 3 and 6 months for the duration of therapy, but we would favour treatment for more

8.7.3 Coccidioidomycosis 1363 than 6 months after resolution of symptoms, and for more than a year with diffuse miliary disease. Conversion to an oral azole is ap- propriate when the patient is improving. Chronic pulmonary coccidioidomycosis This occurs in about 5% of patients with symptomatic primary coccidioidomycosis and may have a fluctuating course over years. Nodular lesions may cavitate, with surrounding infiltrates and fi- brosis. Cavitary disease might be asymptomatic or be associated with rupture and pneumothorax, haemorrhage, or secondary infec- tion. Cavities smaller than 2.5 cm in diameter tend to resolve, while cavities larger than 5 cm persist. Cavities may remain stable for years or become infected with Aspergillus, or fluctuate with inter- mittent infiltrates and fibrocavitary disease. Chronic pulmonary coccidioidomycosis can progressively destroy the lungs and re- quires medical therapy with either fluconazole or itraconazole. The appropriate duration of therapy is uncertain. If large asymptomatic cavities persist for several years, resection should be considered. Coccidioidal mycetoma can occur in pre- existing cavities and is treated by resection. Disseminated coccidioidomycosis Pleura and pericardium may be invaded during pulmonary coc- cidioidomycosis. Haematogenous dissemination occurs within a few months after infection and may involve skin, soft tissue, osteoarticular tissue, and meninges (Figs. 8.7.3.1–8.7.3.3). Papules, nodules, abscesses, verrucous plaques, or ulcers are seen. Medical therapy is often combined with surgical therapy to debulk lesions. In chronic coccidioidomycosis, fluconazole at 400 or 800 mg/day or itraconazole at 200 mg twice daily are used but death may ensue despite intensive medical and surgical intervention. Osteoarticular disease Any bone or joint may be targeted, but those that are weight bearing are more vulnerable (Fig. 8.7.3.4). Infection can destroy the verte- bral body, with collapse and joint instability. Paraspinous abscesses should be drained and, if necessary, the joint(s) stabilized.
Fig. 8.7.3.2 Ulcerative ankle lesion with underlying osteomyelitis in a patient with coccidioidomycosis. Fig. 8.7.3.4 Coccidioidal arthropathy. Copyright R. Hay. Fig. 8.7.3.3 Abscesses on the chest in a patient with coccidioidomycosis. Fig. 8.7.3.1 CT of paraspinous abscess in a patient with coccidioidomycosis.

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