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A Case of Disseminated Coccidioidomycosis

- Autopsy Report -

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Disseminated coccidioidomycosis is a systemic fungal infection that is occuring more commonly and causes high mortality in patients with compromised host defense or debilitated. It is endemic in certain areas of North, Central, and South America. Increasingly, cases are being recognized outside the endemic area, due to travelers who have visited an endemic area. We experienced a case of disseminated coccidioidomycosis, as a reactivation of infection acquired earlier in a patient, who was a former resident of an endemic area.

Key Words : *Disseminated coccidioidomycosis*

INTRODUCTION

Coccidioidomycosis is an acute or chronic pulmonary and disseminated infectious disease caused by the fungus *Coccidioides immitis*, which lives in soil and of which the infectious particle is the arthroconidium. Infection in human results from inhalation of wind borne arthrospores arising from soil sites, and only rarely does direct cutaneous inoculation of the skin occur (Bennet, 1994 ; Stevens, 1995).

Coccidioidomycosis is recovered from certain areas of California, New Mexico, Texas, Central, and South America. It is estimated that in the United States alone about 100,000 people are infected annually (Stevens, 1995).

C. immitis undergoes an alternative form of development when inhaled by a potential host. A recent epidemic of coccidioidomycosis and the possibility of the infection's occurrence in association with human immunodeficiency virus(HIV) infection have renewed interest in the disease(Ampel et al.,1993). The life cycle of *C. immitis* explains why the fungus causes an infectious but not a contagious disease. Person-to-person transmission of coccidioidomycosis has not been reported, and isolation precautions for patients are unnecessary.

Coccidioidomycosis presented lung involvement and two cases have been reported in Korea(Choi et al., 1978 ; Lim et al., 1990). The infection due to *C. immitis* usually results in dissemination beyond the lung in immunocompromised patients, such as malignancy or organ recipients or those with acquired immunodeficiency syndrome (AIDS). Disseminated coccidioidomycosis may involve almost any organ of the body, at one or more site. Widespread milliary dissemination is rare ; patients with rapid dissemination usually die or wax and wane for years. Although disseminated coccidioidomycosis cases were reported, there was no case report in Korea.

Herein, we report a rare case of disseminated coccidioidomycosis including postmortem examination with a review of the literature.

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CASE REPORT

A 63-year-old woman was admitted to the Soonchunhyang University Hospital, because of fever, left shoulder pain, and painful swelling of right second finger for 10 days. She had occasionally suffered from low back pain and left shoulder pain for 1 year.

Three years before entry, she was treated with anti-fungal agent under the diagnosis of pulmonary coccidioidomycosis, which was confirmed by sputum culture and serologic test at a private clinic in California, U.S.A.. But, she had been intermittently prescribed for 6 months.

Her past medical history was noncontributory. She never smoked or drank alcohol. She also complained of general weakness, fever, chill, cough, dyspnea, anorexia, nausea, and loss of body weight.

On admission, her body temperature was 38.6℃, pulse 130/min, blood pressure 130/90mmHg, and respiration rate was 24/min. She had an acutely ill-looking appearance but showed alert mentality. There was no pathologic lesion in her ear, eye, nasal, or oral mucosa. On auscultation of the chest, coarse breathing sounds were heard over both lower lungs with rales. The heart sound was regular without murmur. Her bowel sounds were normal and there was no evidence of hepatosplenomegaly.

On examination of back and extremity, there was tenderness on both costovertebral angles, painful swelling was present on the right second finger with tenderness.

Laboratory finding on admission showed that the white blood cell count was 19,800/mm^3 with 94 percent neutrophils and 4 percent bandforms, hemoglobin was 8.3gm/dL, hematocrit was 24.2% and the platelet count was 513,000/mm^3. The erythrocyte sedimentation rate was 57mm/hour. Her urine was normal. Values were normal for sodium, potassium, calcium, blood urea nitrogen, creatinine, glucose, GOT, GPT, bilirubin and alkaline phosphatase. But, albumin was 1.9mg/dL. The blood, urine, sputum and bone marrow culture for *C. immitis* were negative.

Chest X-ray and computerized tomography revealed numerous nodules in the entire lung fields (Fig. 1, 2). Under the diagnosis of disseminated coccidioidomycosis, amphotericin B was prescribed. However, no improvement was noted. On the fourth hospital day, the dyspena and fever aggravated and the patient was transfered to an intensive care unit. On the sixth hospital day, the patient expired. Autopsy was then performed.

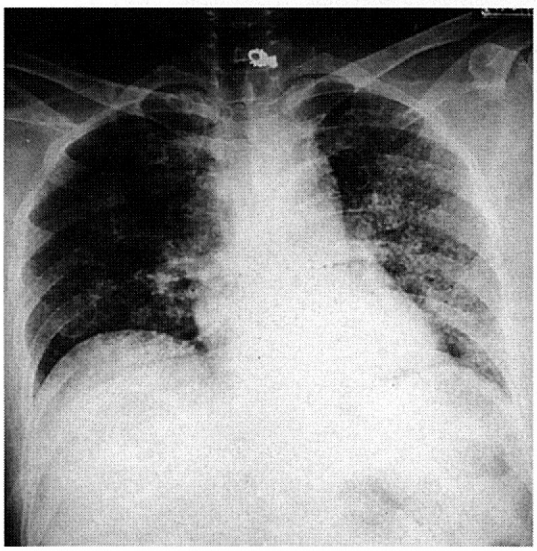

Fig. 1. The chest roentgenogram taken on admission revealed diffuse scattered, numerous discrete nodules in the entire both lung fields.

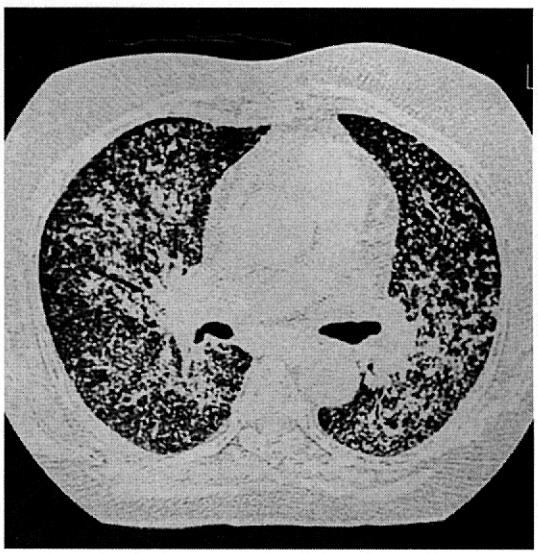

Fig. 2. Chest high resolution computed tomography showed 1-2mm sized well-defined nodules of the entire lungs. In addition to these nodules, thickening of parahilar broncho-vascular bundles and intralobular septi. But, relative scanty interlobular septal thickening was found.

POSTMORTEM FINDINGS

Macroscopic examination

The body was a 63-year-old obese woman, weighing 48kg and measuring 154cm in height. The autopsy was done 12 hours after death. The head circumference was 45cm, the chest circumference was 95cm, and the abdominal circumference was 84cm. A discolored ulcerative skin lesion was found on the right index finger with purulent discharge. Another disclored skin lesion was noted on the right pretibial area. The midline incision was done. Opening the thorax, about 100ml of pleural fluid was present. There was slight adhesion dissecting the lungs. The right and the left lungs were heavy and edematous, weighing 1,000gm and 850gm respectively. The pleural surface was mottled with many yellow nodules. On palpation it was diffusely rubbery. The cut surface showed multiple miliary yellow nodules throughout the both entire lungs(Fig. 3). A small amount of frothy edema fluid was expelled out from the trachea. Multiple enlarged tracheobronchial lymph nodes were noted. There was 15cc pericardial fluid. The heart and great vessels were unremarkable except for mild atherosclerosis. The thymus was atrophic.

Opening the peritoneal cavity there was small amount of ascitic fluid. The liver was enlarged, pale brown and heavy, weighing 1,175gm. On section the cut surface showed a nutmeg pattern of centrilobular congestion and peripheral fatty change. The spleen was markedly congested, weighing 120gm. The right and left kidneys weighed 180 and 170gm respectively. On section the cut surface showed pale cortex and congested medulla with multiple brownish yellow nodules from the cortex to the medulla, measuring 0.5 to 3cm in diameter. Both adrenals were congested, weighing 6gm and 4gm and otherwise unremarkable. The stomach was air-distended. The small and large intestines were unremarkable. There was an appendix, retrocecally. The rectum was filled with dark greenish loose feces.

Microscopic findings

Sections of the both lungs showed multifocal necrotizing granulomatous inflammation(Fig. 4). The air spaces were frequently destroyed and replaced by microabscesses. Around the central necrotic area aggregation of epitheloid cells, multinucleated giant cells, and neutrophils were present. Innumerable variable sized large fungal spores were noted freely in the interstitium as well as in the alveolar spaces and within the cytoplasm of multinucleated giant cells(Fig. 5). Those organisms were thick walled nonbudding spherules of 20-60㎛ in diameter, filled with small endospores. They were seen easily on

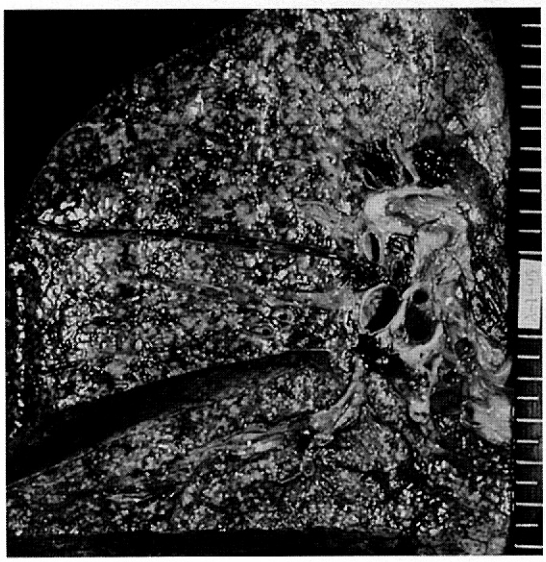

Fig. 3. The cut surface of the right lung discloses multiple miliary nodules on the entire right lung.

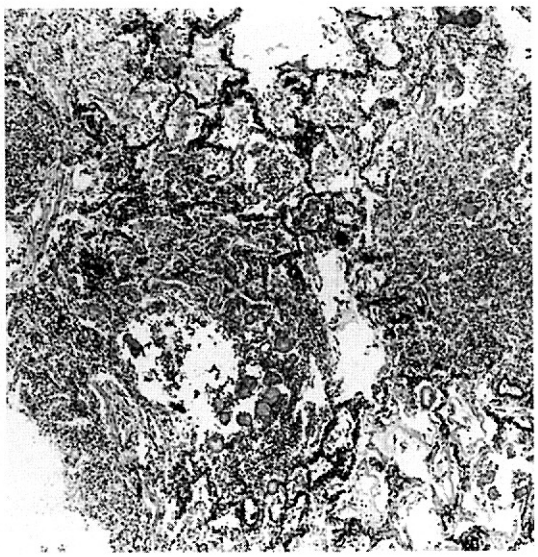

Fig. 4. Microphotograph of the lung demonstrates necrotizing granulomatous inflammation (H-E, x100).

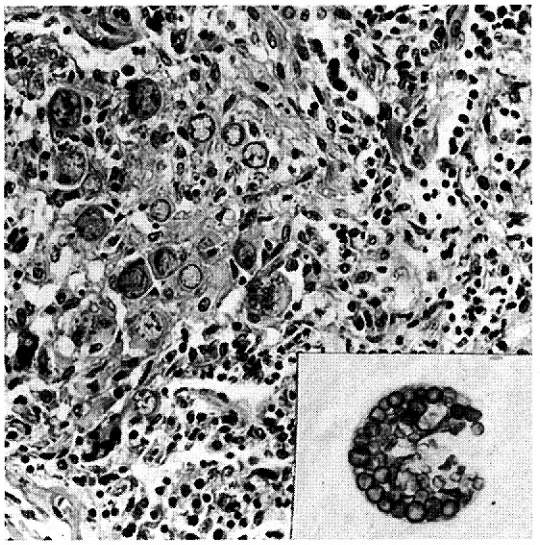

Fig. 5. High power view discloses a granuloma containing many thick walled nonbudding spherules filled with endospores (H-E, x400 ; Inset : Gomori's methenamine silver, x1,000).

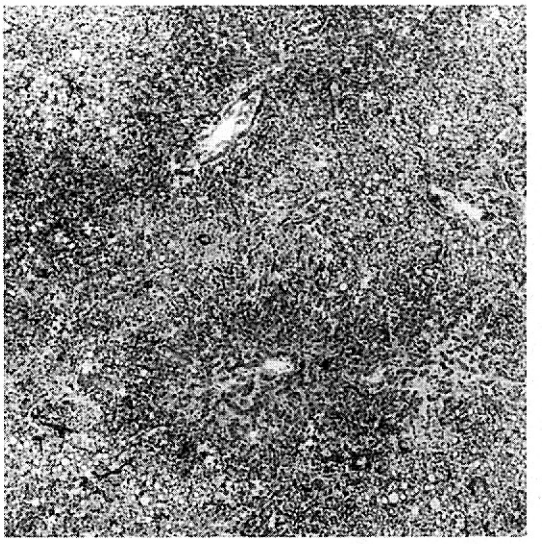

Fig. 6. Low power view of the liver discloses centrizonal necrosis, periportal fatty change and a few granulomas (H-E, x40 ; Inset : H-E, x200).

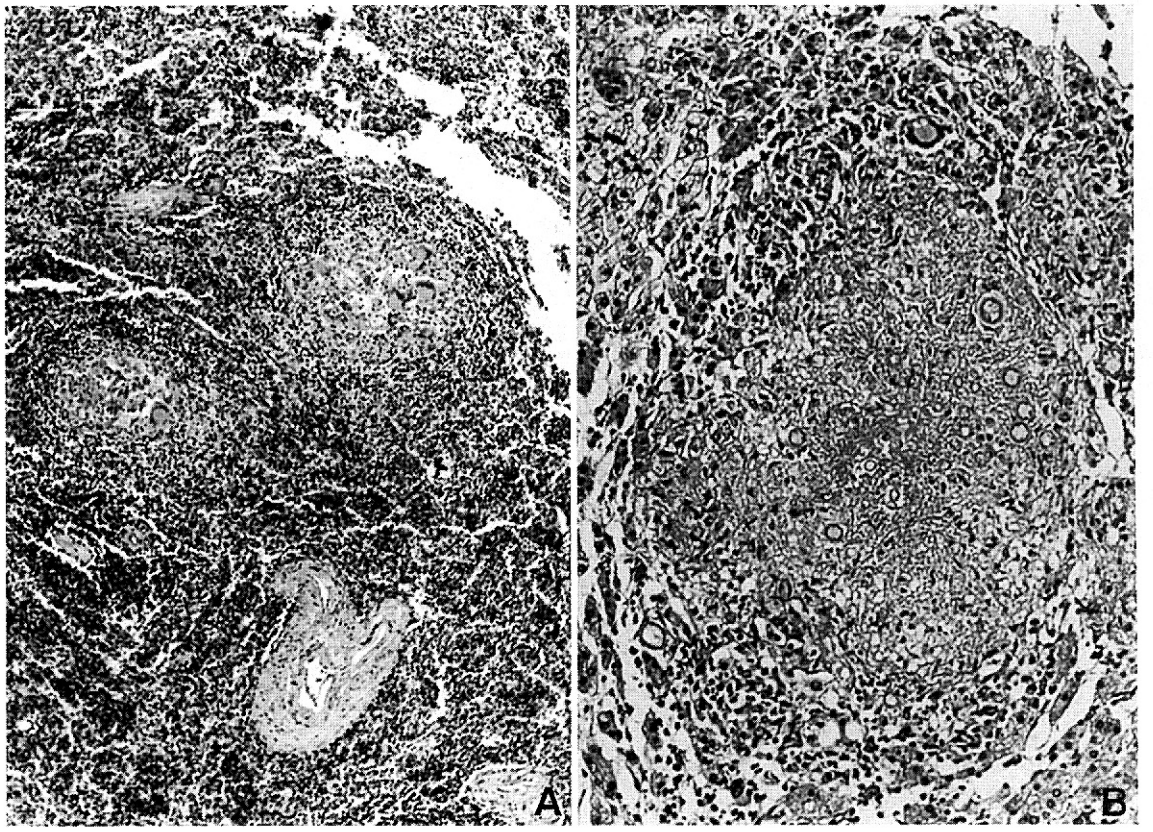

Fig. 7. Sections of spleen(A) and adrenal gland(B) show multiple granulomas containing spherules (H-E, A:x40, B:x100).

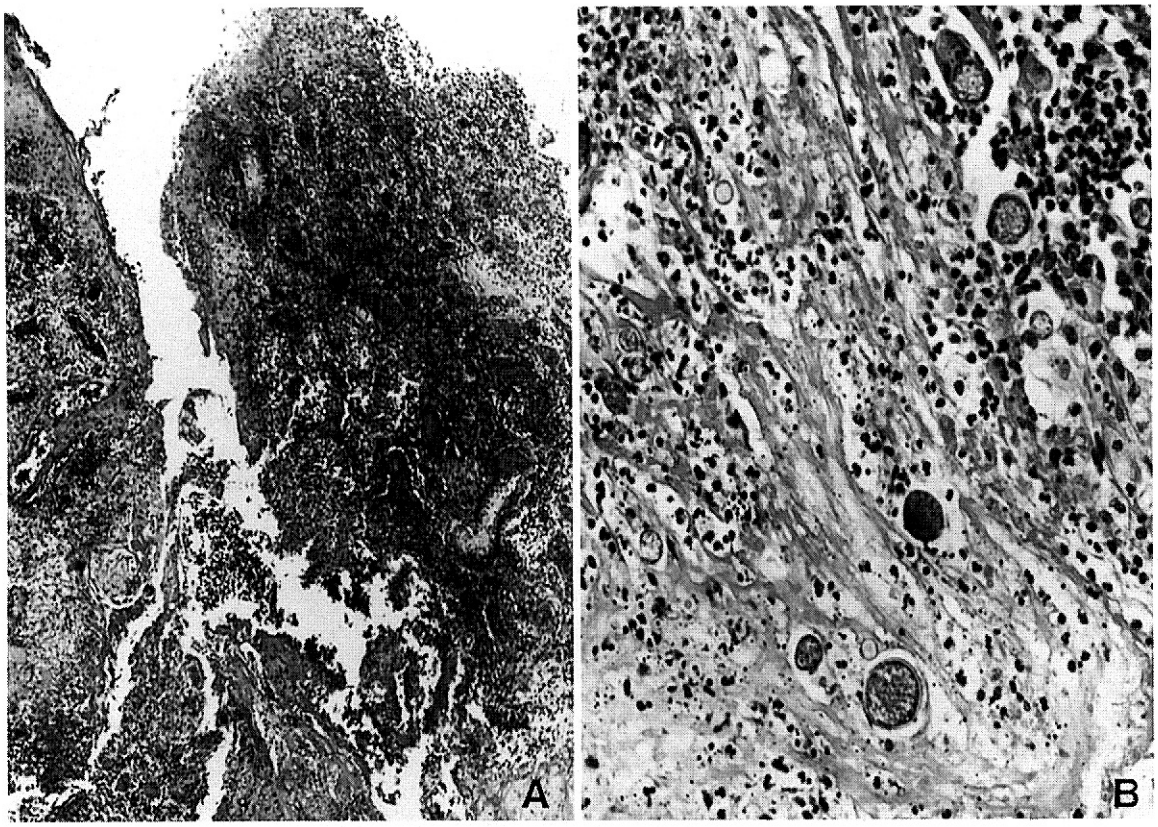

Fig. 8. The section of skin shows ulceration with necrotizing granulomatous inflammation(A) containing many spherules filled with endospores(B)(H-E, A:x40, B:x400).

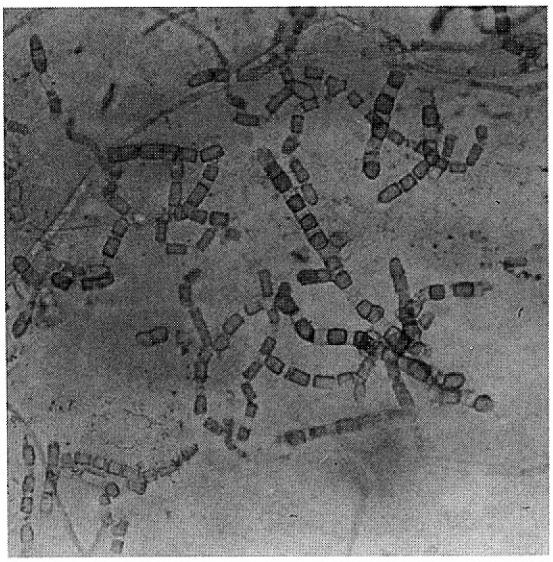

Fig. 9. Deeply stained arthrospores separated by clear space were identified (lactophenol cotton blue stain, x100).

routine H-E stain. Special stains such as periodic acid-Schiff stain and Gomori's methenamine silver demonstrated the large spherules and endospores very well. Some of the spherules were ruptured and multiple endospores were pouring out. The tracheobronchial lymph nodes were largely replaced by hyalin nodules and had multiple organisms.

Sections of the liver showed centrizonal hemorrhagic necrosis and periportal fatty change(Fig. 6). A few granulomas containing fungal spherules filled with endospores. Renal tubules were lined by necrotic epithelial cells. Section of the spleen(Fig. 7A) and the adrenal glands(Fig. 7B) demonstrated multiple granulomas containing fungal spherules in addition to congestion. Section of the skin from the index finger showed ulceration and necrotizing granulomatous inflammation extending deep into the periosteum. Numerous characteristic fungal spherules filled with endospores were found(Fig. 8).

Postmortem culture

Postmortem blood culture from the right heart disclosed *Escherichia coli*. Postmortem tissue culture from the lung disclosed a white cottony colony on Sabouraud dextrous agar. Deeply stained arthrospores separted by clear space were found on lactophenol cotton blue stain(Fig. 9), consistent with *C. immitis*.

DISCUSSION

In this patient with disseminated disease, fever, chill, malaise, cough, dyspnea, and anorexia were the major symptoms. Her symptoms were compatible with disseminated coccidioidomycosis, based on thick walled nonbudding spherules filled with small endospore revealed by lung and liver examination. The typical manifestation is a pulmonary infection accompanied by systemic symptoms, such as fever, weakness, sweating, cough, sputum production, chest pain, anorexia, and arthralgia. The acute infection usually resolves without proper treatment, although the illness may last for several weeks. Occasionally, the acute respiratory infection does not resolve, and a dissemination or chronic pneumonia develops(Lim et al., 1990). A minority of patients develop complications or progressive forms of infection that display a broad variety of manifestrations and pose difficult problems for the clinician. Symptomatic extrapulmonary disease develops in about 1 of 200 people infected with C. immitis. Rarely, widespread rapid dissemination may occur with a miliary and usually fatal picture. Dissemination should be suspected when fever, malaise, hilar or paratracheal lymphadenopathy, elevated sedimentation rate, and high complement fixation titers show abnormal persistence in patients with pulmonary coccidioidomycosis. Disseminated infection is more frequent in men, pregnant woman, nonwhite people, and immunocompromised patients including those with AIDS.

Coccidioidomycosis in AIDS patients living in the coccidioidal endemic area is not uncommon and that coccidioidomycosis has wider range of manifeatations in HIV-infected patients than previously recognized.

High mortality was seen in those with diffuse pulmonary disease and in those with low CD4 counts (Fish et al., 1990).

The host defence mechanisms are incompletely understood, but available information indicates that they are cell mediated. Cell-mediated immunity is characteristically impaired in patients with disseminated coccidioidomycosis (Galgiani et al., 1978). The defect may be specific for coccidioidal antigen(delayed hypersensitivity skin test or in vitro lymphocyte transformation response)(Frey and Drutz, 1986; Galgiani, 1986), or it may be generalized to other antigen as well(Kaplan et al., 1980). In the disseminated form of disease, the bone, skin, subcutaneous tissue, meninges, joints, and other sites are common sites of infection. Technetium diphosphate bone scan is a sensitive screening method. The ankle and knees are most commonly involved. Synovial biopsy may be required for the diagnosis of dissemination. Skin lesions are variable, but wartlike nodules are the most common.

The diagnosis is firmly established by demonstrating *C. immitis* from sputum, aspirates of infected areas, and resected deep tissue. In biopsy or autopsy tissue specimen, a mature spherule of *C. immitis* with endospore is pathognomonic of infection and can be identified with a variety of strains. The surrounding tissue may show a granulomatous reaction. The mycelial form of the fungus has undemanding growth requirement; it may appear on any growth media and after incubation at most conditions. Culture of *C. immitis* represent a severe biologic hazard, and should be handled only by experienced personnel at laboratories with appropriate safety equipment and procedure(Johnson et al., 1964). The organisms can be seen in or grown easily from pus and can be detected in other infected material, such as sputum, urine and infected aspirates. Cytologic examination and chemical digestion of purulent sputum before culture are useful.

Serologic tests are very helpful in coccidioidomycosis. The originally described serologic procedures for detecting coccidioidal antibodies were the tube precipitin and complement fixation tests. More recently, double immunodiffusion procedures have been devised to mimic the original tests and are available commercially. These tests are very specific and provide strong evidence for recent or active coccidioidal infection. There were also ELISA procedures using spherule-derived antigens for earlier detection of coccidioidal infection (Galgiani et al., 1991). An elevated IgG serum antibody titer is a mar-

ker of disseminated, extrapulmonary disease. Specific IgG antibody titer also reflects the course of the disease and is thus helpful in determining whether it is progressing or improving. Routine serologic testing can prevent a delayed diagnosis of their rapidly fatal infection.

Appearance of delayed hypersensitivity to antigen of *C. immitis* is most common in those clinical forms of disease with good prognosis. Skin-test reactions to coccidioidal antigen become positive soon after the development of symptoms in virtually all people with primary infection, and cross reactions with other infection are rare. *Coccidioides immitis* has an enhanced invasive potential comparable to that of other fungal pathogens in the host whose immunity is impaired by disease or immunosuppressive therapy.

In this case, amphotericin B might have not have contributed to the improvement of coccidioidomycosis because it was too late to cure of her illness. Most patients with symptomatic primary infection are usually self limited. But patients with more serious forms of coccidioidal infection should receive chemotherapy and treatment for only a few weeks is likely to resolve the abnormalities associated with acute infection. In patients with disseminated diseases, prolonged chemotherapy is always indicated. Amphotericin B therapy should be continued for a total of two to three months, or until the disease becomes inactive. Itraconazole is an effective drug to treat coccidioidomycosis with a wide safety margin, as an alternative. It is well tolerated, and the incidence of relapses is low (Diaz et al., 1991). Local administration or irrigation of amphotericin B or miconazole to inflammated site, such as joints or pleural spaces, may rapidly improve the infection. This patient may need more meticulously careful management.

The importance of the immune response in control of the infection, as described, has led to approaches directed to manipulation of the host response to prevent disease or to treat it. Although vaccines are currently under intense study, an effective vaccine is still a hope. Synthetic immunomodulators or those produced by recombinant- DNA techniques may offer a future approach to therapy.

Also we recommend that intensive antifungal treatment should be done for every patient suspective of coccidioidomycosis, one with debilitated, compromised host defence, or one who visited an endemic area.

REFERENCES

Ampel NM, Dols CL, Galgiani JN. *Coccidioidomycosis during human immunodeficiency virus infectio : result of a prospective study in a coccidioidal endemic area. Am J Med 1993 ; 94 : 235-40.*

Bennet JE. *Fungal infections. In : Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. Harrison's principles of Internal medicine, 13th ed. New York : McGraw-Hill, 1994 ; 857-8.*

Choi TY, Kim CW, Kim KH. *A case of coccidioidomycosis. Korean J Pathol 1978 ; 12 : 199-206.*

Diaz M, Pnente R, Hoyas LA. *Itraconazole in the treatment of coccidioidomycosis. Chest 1991 ; 100 : 682-4.*

Fish DG, Ampel NM, Galgiani JN, Dols CL, Kelly PC, Johnson CH, Pappagianis D, Edwards JE, Wasserman RB, Clark RJ, Antoniskis D, Larsen RA, Englender SJ & Petersen EA. *Coccidioidomycosis during human immunodeficiency virus infection. A Review of 77 patients. Medicine 1990 ; 69 : 384-91.*

Frey CL, Drutz DJ. *Influence of fungal surface components on the interaction of Coccidioides immitis with polymorphonuclear neutrophils. J Infect Dis 1986 ; 153 : 933-43.*

Galgiani JN. *Inhibition of diifferent phases of Coccidioides immitis by human neutrophils or hydrogen peroxide. J Infect Dis 1986 ; 153 : 217-22.*

Galgiani JN, Grace GM, Lundergan LL. *New serologic test for early detection of coccidioidomycosis. J Infect Dis 1991 ; 163 : 671-4.*

Galgiani JN, Isenberg RA, Stevens DA. *Chemotaxigenic activity of extracts from the mycelial and spherule phases of Coccidioides immitis for human polymorphonuclear leukocytes. Infect Immun 1978 ; 28 : 944-9.*

Johnson JE III, Perry JE, Fekety FR, Kadull PJ, Cluff LE. *Laboratory-acquired coccidioidomycosis : a report of 210 cases. Ann Intern Med 1964 ; 60 : 941-56.*

Kaplan JE, Zoschke D, Kisch AL. *Withdrawal of immunosuppressive agent in the treatment of disseminated coccidioidomycosis. Am J Med 1980 ; 68 : 624-8.*

Lim GE, Woo JH, Chung YT, Uh ST, Park CS. *A case of pulmonary coccidioidomycosis. Tuberc Respir Dis (English abstract) 1990 ; 37 : 440-4.*

Stevens DA. *Coccidioides immitis. In : Mandel GL, Bennet JE, Dolin R'eds. Principles and practice of infectious diseases, 4th ed. New York: Churchill Livingstone, 1995 ; 2365-75.*