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The First Imported Case of Pulmonary Coccidioidomycosis in Korea

Coccidioidomycosis is an endemic disease found in the southwestern part of North America. Travellers who visit the endemic area may carry the infection. We report a case of pulmonary coccidioidomycosis in a 74-year-old woman. She was healthy before visiting Arizona, U.S.A twice. After returning home, she began to complain of intermittent dry coughing. The symptom was mild, however, and she was treated symptomatically. Later a chest radiograph, which was taken 4 years after the onset of the symptom, showed a solitary pulmonary nodule in the right upper lobe. By percutaneous needle aspiration, a few clusters of atypical cells were noted in the necrotic background. A right upper and middle lobectomy was done. A 1.5×1.5×1.2 cm sized tan nodule was present in otherwise normal lung parenchyma. Microscopically, the nodule consisted of aggregates of multiple solid granulomas inside of which was mostly necrotic. Neutrophils and nuclear debris were scattered along the periphery of the necrotic foci. Numerous multinucleated giant cells were associated with the granulomas. In the necrotic area, mature spherules of *Coccidioides immitis*, which were 30-100 μm in diameter, were present. They contained numerous endospores which ranged from 5 to 15 μm and were also noted in multinucleated giant cells. The diagnosis of coccidioidomycosis was made. She is doing well after the resection.

Key Words : *Coccidioidomycosis; Lung diseases; Diagnosis*

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INTRODUCTION

In America, coccidioidomycosis is a common fungal infection. It is estimated that 100,000 new cases occur yearly and approximately 70 deaths are reported annually (1). It is endemic in the deserts of the southwestern United States, northern Mexico, and parts of Central and South America (1). Many tourists and visitors acquire the infection as well as inhabitants (2). When they return home with the illness, considerable diagnostic confusion may occur. Here, we report the first case of pulmonary coccidioidomycosis diagnosed in Korea.

CASE REPORT

A 74-year-old Korean woman visited her daughter who lived in Phoenix, Arizona, U.S.A., for several months. After returning home, she began to complain of intermittent dry coughing and night sweating. The symptom was mild, however, and she was treated symptomatically. When she visited her again in the following year, she complained of dry coughing and nocturnal sweating again. After returning, the symptom disappeared. On a routine chest radiograph taken 4 years after the onset of the symptom, a 1.5 cm-sized pulmonary nodule was detected in the anterior segment of the right upper lobe (Fig. 1). The nodule was solitary without any other parenchymal lesion or associated lymphadenopathy. By percutaneous needle aspiration cytology, a few clusters of atypical cells were noted in the necrotic background (Fig. 2). A malignancy was suggested, and a right upper and middle bilobectomy was done. In the upper lobe, a tan nodule of 1.5×1.5×1.2 cm was present; it was irregularly outlined and had central necrosis. By microscopic examination, the lesion consisted of multiple granulomas with central necrosis and numerous multinucleated giant cells (Fig. 3). At the periphery of the necrosis, numerous neutrophils and nuclear debris were present (Fig. 4). In the necrotic area, irregular spore-like structures were noted. On Periodic Acid-Schiff and Gomori's methenamine silver staining, degenerating ma-

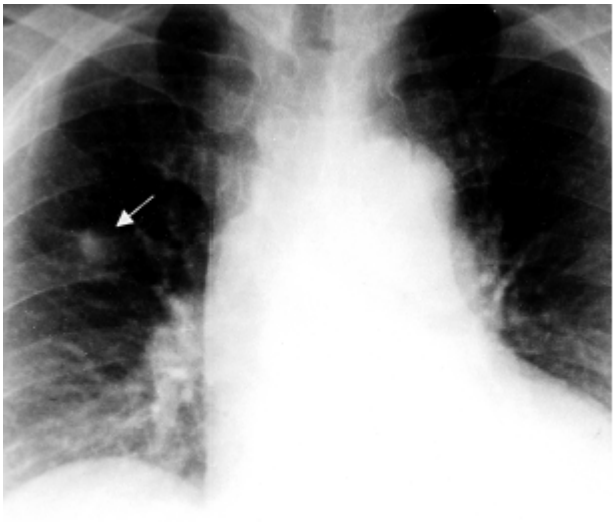

Fig. 1. Chest radiograph. Note a 1.5 cm-sized solitary pulmonary nodule in the right upper lobe (arrow). The lung parenchyma is otherwise unremarkable.

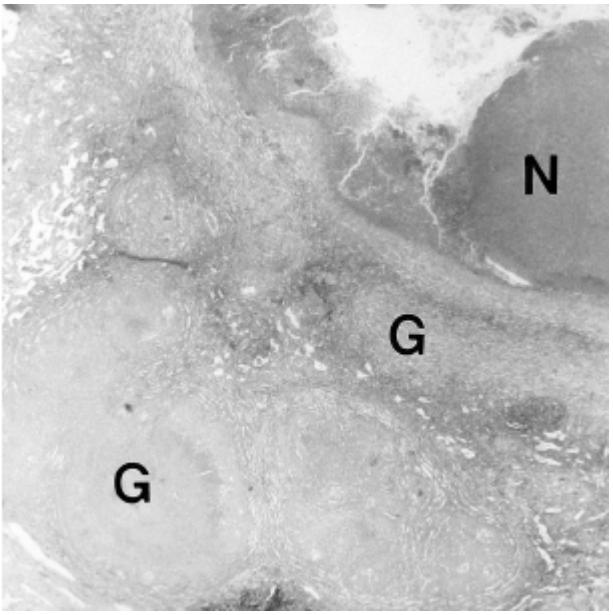

Fig. 3. The lesion consisted of aggregated granulomas (G) with central necrosis (N) (H & E, ×20).

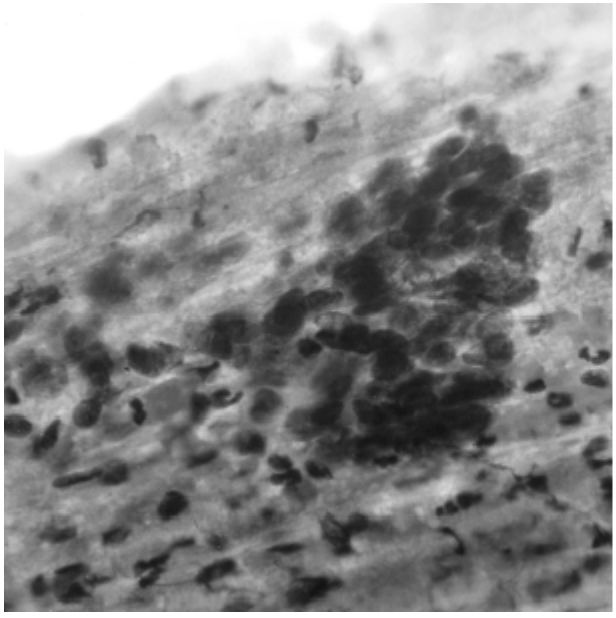

Fig. 2. Percutaneous needle aspiration cytology: A cluster of atypical cells in the necrotic background with acute inflammation (H & E, × 400).

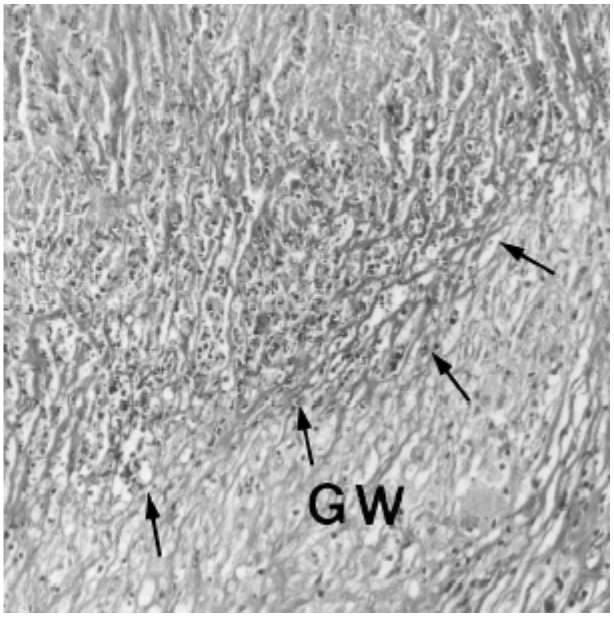

Fig. 4. In the necrotic area, which is confined by the granuloma wall (GW), numerous neutrophils and nuclear debris are present (arrows) (H & E, ×100).

ture spherules of *Coccidioides immitis* were scattered (Fig. 5). They measured 50-100 μm in diameter, and contained numerous endospores. Endospores varied considerably in size, ranging from 5 to 15 μm, and the wall measured from 1 to 2 μm in thickness. The variable size of endospores appeared to be due to a degenerative change. There were also immature spherules without endospores. Endospores were noted in the multinucleated giant cells as well. Upon reviewing the aspi-

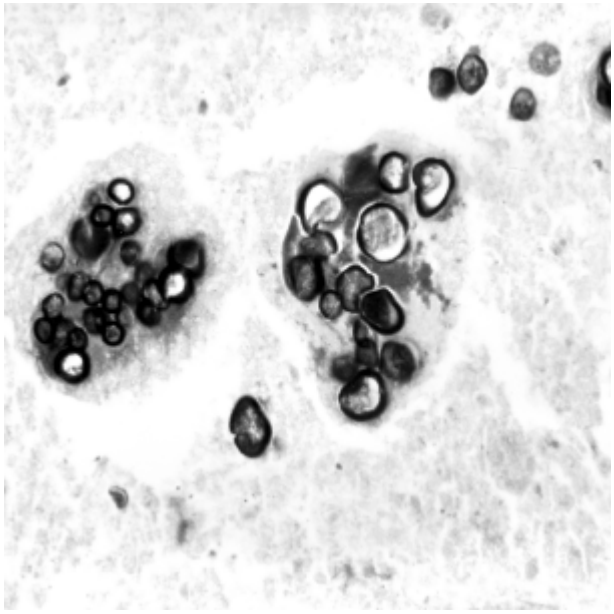

Fig. 5. Mature spherules of *C. immitis* containing numerous endospores. The outer walls are degenerated by inflammation. Endospores vary considerably in size (PAS stain, ×400).

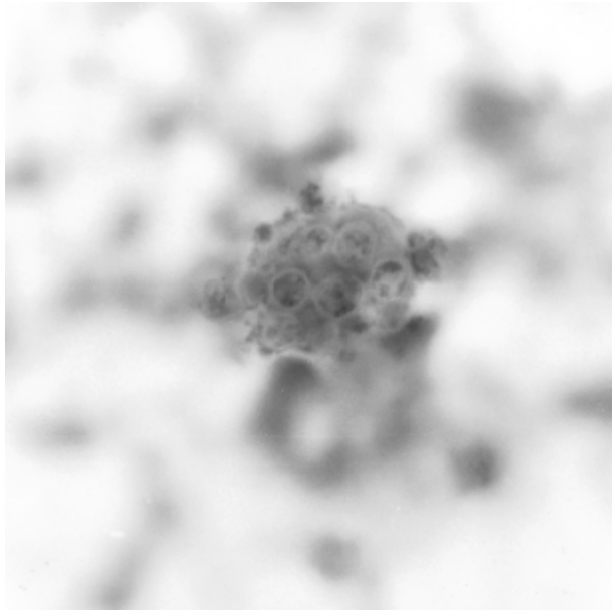

Fig. 6. A mature spherule in the aspirate. Note numerous endospores in the spherule. The walls are not stained (H & E stain, ×400).

ration cytology specimen, a spherule containing endospores was identified (Fig. 6). After the surgery, she is doing well without additional medical treatment.

DISCUSSION

As more people travel around the world, many diseases will not remain truly endemic in nature. When patients come back home carrying those "endemic" diseases, various problems may be posed in the diagnosis and treatment of the unexpected diseases. Coccidioidomycosis would certainly qualify as one of those concerns.

Coccidioidomycosis is a disease caused by the dimorphic fungus, *C. immitis*. The inhalation of arthroconidia initiates the pulmonary infection. Each inhaled arthroconidum in the lung develops into a spherule in which numerous endospores are formed. These endospores are released when the spherule ruptures, resulting in rapid growth of organisms repeating the same maturating cycle within the host (3, 4).

The acute phase of coccidioidomycosis is usually asymptomatic or presented with mild symptoms. Approximately 40% develop symptoms of a primary infection 1-3 weeks after exposure (2). The symptoms resemble a lower respiratory infection and/or systemic illness; cough, chest pain, malaise, fever, chills, night sweat, anorexia, and arthralgia may be present. Approximately 2-5% of patients develop chronic pulmonary coccidioidomycosis, in which nodule or cavity formation, lymphadenopathy, chronic progressive pneumonia or miliary infiltrates may develop (4, 5). Among the manifestations, coccidioidal nodule is the most common (5). The primary coccidioidomas are frequently located in lower lobes; however, no other location is exempt (5). They may develop in the pleura as well (5). When coccidioidomas develop, the patients are often asymptomatic. However, the "coin lesion" on a chest X-ray would pose a diagnostic problem (5, 6).

For differential diagnosis, a careful recording of history, especially of overseas travels, is of prime importance. Fine-needle aspiration cytology could be applied effectively (5). Unless coccidioidomycosis is suspected clinically, however, the interpretation of aspiration cytology could be misleading, especially in non-endemic setting (6). A mature endosporulating spherule is pathognomonic. Characteristic spherules distinguish *C. immitis* from other encountered fungal organisms such as *Histoplasma* and *Cryptococcus*. Mature spherules, however, may not come across in the aspirate. When outer walls of spherules are digested by neutrophils, only scattered endospores may be present without typical spherules (6). Endospores vary in size considerably and frequently degenerated by inflammation; thus, they may not be recognized as specific organisms by pathologists who are not familiar with them.

Atypical epithelial changes may pose another diagnostic problem. Atypical reactive bronchial epithelial cells or epithelioid cells from the granulomas in the necrotic background may suggest a malignancy (5, 6). Other diagnostic methods such as sputum culture, coccidioidin skin test (positive in

60%), serology, and complement fixing antibody may be useful in such a situation (2). When diagnostic measures are not available, surgical excision and histologic confirmation is to be followed.

In human lungs, liberated endospores induce an intense neutrophil response, while spherules stimulate a granulomatous response mostly (7). Thus, granulomas caused by *C. immitis* frequently have central necrosis, which may be reminiscent of other granulomatous diseases such as tuberculosis. Unlike tuberculomas, however, granulomas in coccidioidomycosis are usually associated with neutrophilic infiltration, as was observed in this case. When acute inflammation and spores of variable size are present in a granuloma with central necrosis, coccidioidomycosis should be suspected and mature spherules should be sought for. Endospores are found in multinucleated giant cells as well.

The tissue reaction may be dependent on several factors; 1) differences in antigenicity of cell walls in three cell types (arthroconidia, spherules, and endospores), 2) amount of *C. immitis* present in tissue, and 3) differences in the state of the immunological defense mechanism of the host (7). When healthy persons are infected, the disease is mostly subacute or self-limited. But serious conditions such as fungemia, diffuse pulmonary involvement, or extrathoracic infections may be encountered in diabetics, pregnant women and immunocompromised patients with lymphoma, organ transplantation, or HIV infection (3, 6, 8). In those cases, systemic chemotherapy is indicated.

Whereas most patients with primary infections recover spontaneously, surgical removal of pulmonary cavitary disease is indicated in the presence of persistent, recurrent, or severe hemoptysis or intrapleural rupture. Once the disease has spread outside the lungs involving such areas as musculoskeletal or central nervous system, a chemotherapy becomes needed. To prevent systemic dissemination, chemotherapy may be applied to patients with high complement fixing antibody titer, persistent symptoms over 6 weeks, prostration, or extensive pulminary involvement (9).

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