

# Invasive Aspergillosis in a Patient with Systemic Lupus Erythematosus

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## Abstract

Invasive aspergillosis, a life-threatening infection, most often occurs in severely immunocompromised patients and in patients with granulocytopenia. It has rarely been described in patients with systemic lupus erythematosus. We report a patient who was diagnosed as systemic lupus erythematosus 2 months earlier and was given high dose of corticosteroids to control her vasculitis and nephritis. High spike fever, dyspnea and non-productive cough developed one week before admission. A chest radiograph showed patchy infiltrations in the right middle and right lower lungs. Sputum examination for bacteria and mycobacterium were negative, but scatter hyphae of fungi were observed and was considered as contaminant. Intravenous ceftazidime and netilmicin were prescribed without response. The chest radiograph showed progressive infiltrations in the right and left lungs. The patient died from respiratory failure. Sputum cultures grew *Aspergillus fumigatus*. A necropsy of the lung showed invasion of aspergillus in the lung tissue. (*J Infect Dis Antimicrob Agents* 1997;14:97-100.)

## INTRODUCTION

Increased susceptibility to infection is well recognize in patients with systemic lupus erythematosus (SLE). Infection is still the most common cause of morbidity and mortality (1-3). Immunological disturbances, either from the disease itself or from immunosuppressive therapy, or complications of the disease such as uremia are contributing factors for infection. Both common pathogens seen in healthy individuals and opportunistic pathogens have been described. These organisms include *Staphylococcus aureus*, *Klebsiella* spp., *Salmonella* spp., *Streptococcus* spp., *Cryptococcus neoformans*, *Varicella zoster*, *Candida* spp., *Nocardia* spp., *Mycobacterium tuberculosis* and *Pneumocystis carinii* (1-7). Surprisingly, invasive aspergillosis, a common fungal infection in immunocompromised patients has rarely been described in SLE. We report here a case of fatal invasive aspergillosis in a patient with SLE.

## CASE REPORT

A 45-year-old woman was admitted to the Chiang Mai University Hospital because of dyspnea and fever. She was diagnosed as having SLE two months earlier at the Ramathibodi Hospital in Bangkok when she presented with intermittent fever, weight loss, alopecia, pleuritic chest pain, Raynaud's phenomenon, photosensitive rashes and vasculitic lesions on her palms and soles. Significant laboratory tests were proteinuria with cellular cast, positive antinuclear, anti-ds DNA and anti-Sm antibodies. Prednisolone 60 mg/day orally was prescribed with improvement of the cutaneous lesions.

One week before admission, she began to have fever, dyspnea and non-productive cough. Her vital signs showed a temperature of 38.0°C, blood pressure of 130/70 mmHg, pulse rate of 110/min. and respiratory rate of 24/min. Significant physical examinations were dyspnea, pallor,

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oral thrush, crepitation and increased vocal resonance at the right lower lung field, discoid lesions on her ears and elbows, and vasculitic lesions on her palms and soles.

A complete blood count showed a hemoglobin of 8.8 g/dL, hematocrit of 22 vol%, white blood cell (WBC) count of 12,680 cells/mm<sup>3</sup> with polymorphonuclear cells 89 percent, lymphocytes 8 percent and monocytes 3 percent. Urinalysis showed 3<sup>+</sup> proteinuria with cellular casts. A 24-hour urine protein was 1.3 g/day. Multiple patchy infiltrations at right middle and right lower lungs were seen in the chest radiograph (Fig. 1). Sputum was inadequate but scatter hyphae of fungi were observed in Gram stained smears of the bronchial secretion and was initially interpreted as contaminant as seen in oral candidiasis. Serum iron and total iron binding capacity were 32 (normal 50-130 µg/dL) and 130 (normal 150-450 µg/dL) respectively. Direct Coombs' test was positive. Liver function tests showed mild hypoalbuminemia, 2-4 time elevation of serum aminotransferase and alkaline phosphatase enzymes. Other laboratory tests including renal function, serum complements, stool occult blood and tuberculin skin tests were normal or negative.

Intravenous cefuroxime was prescribed for her pneumonia without response. A follow-up chest radiograph showed increasing pulmonary infiltrates in the right middle, right lower and left upper lungs, with some cavitations (Fig. 2). The antibiotic was changed to ceftazidime and

netilmicin. Ten days after admission she developed acute respiratory failure, cardiovascular collapse, coma and sepsis with multiple organ failure. A computed tomography of the head showed multiple hypodensity in the brain parenchyma compatible with metastatic infections. Despite aggressive supportive therapy, she died on the 16th day of hospitalization. Post-mortem necropsy showed septated branching hyphae consistent with *Aspergillus* spp. in the lung and brain tissues (Fig. 3). Sputum cultures grew *Aspergillus fumigatus*. The culture result was available after her death.

## DISCUSSION

Invasive aspergillosis is a life-threatening infection that occurs most often in immunocompromised patients. These include patients with malignancy, organ transplant, on chemotherapy, chronic renal failure, chronic alcoholism, diabetes mellitus, chronic liver disease and the acquired immunodeficiency syndrome (8). However, it has been occasionally described in normal healthy individuals (9).

Aspergilli are the most common saprophytic fungi. They are common in the air and area where organic debris are prevalent. In immunocompetent patients, it can produce allergic reaction such as asthma, allergic bronchopulmonary aspergillosis or colonize in pre-existing cavity or cause superficial skin infection. But in immunocompromised patients it can invade into deep subcutaneous tissue. Invasive aspergillosis is a condition diagnosed only by

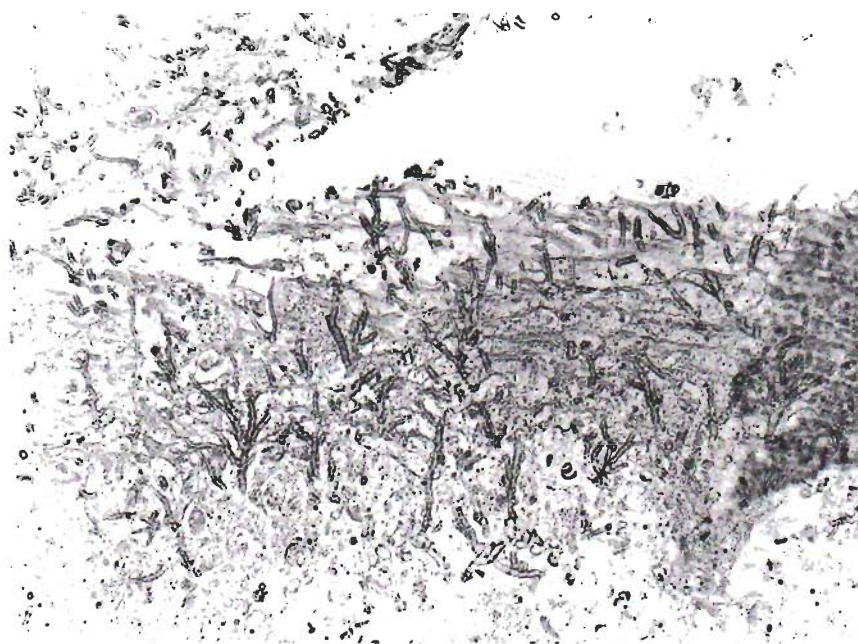


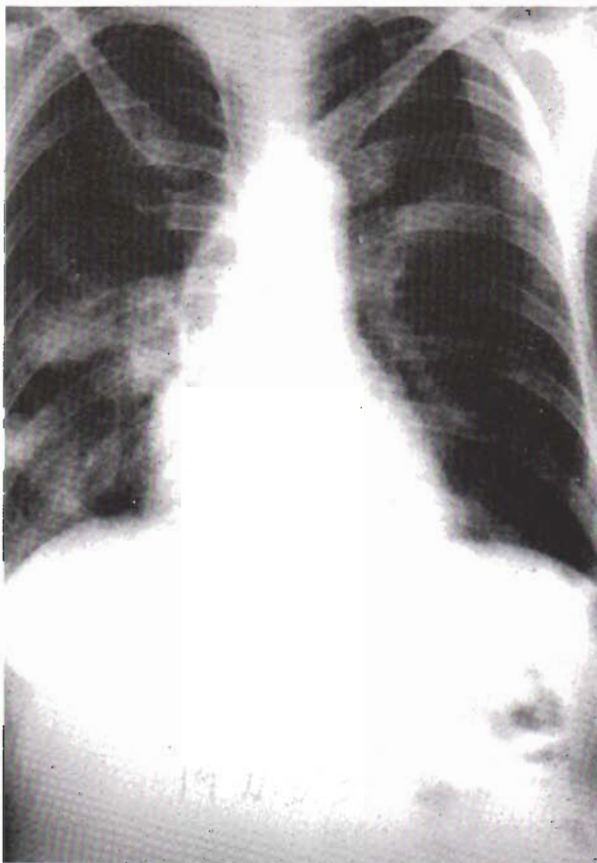
Fig. 1 A chest radiograph showing patchy infiltrations at the right middle and right lower lungs.

demonstrating the aspergillus hyphae in tissue sections, preferably with culture confirmation (8).

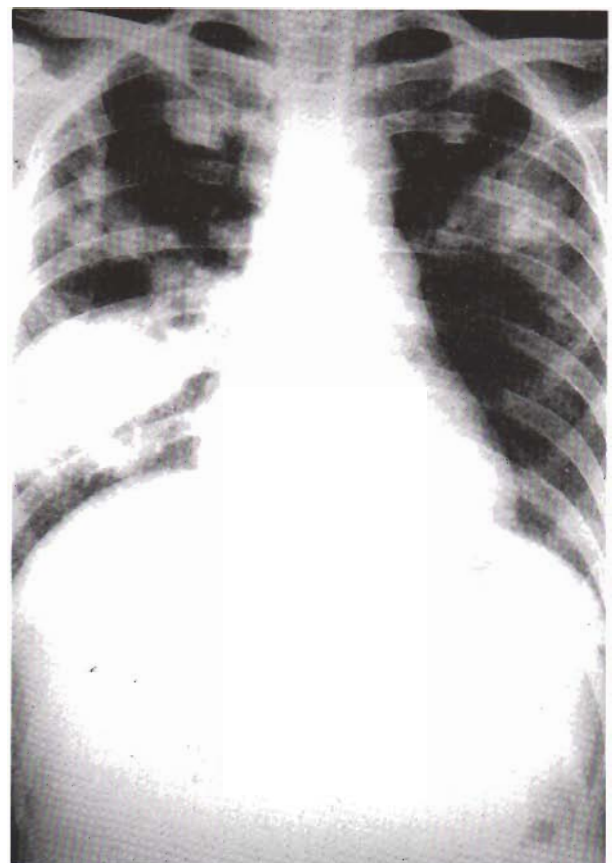
Gonzalez-Crespo MR et al, in 1995 (10), reported 2 cases of invasive pulmonary aspergillosis and reviewed the literature between 1957 and 1994. Twenty-one cases were identified, but only 8 cases had details of clinical information for analysis. The mean age of the patients was 30 years and the mean interval between the diagnosis of SLE and the development of aspergillosis was 61 months. *A. fumigatus* was isolated in the majority of cases. Dyspnea and non-productive cough were the most common presenting symptoms. Pre-mortem diagnosis was suspected in 2 cases. Ninety-five percent of the patients died. Among 8 patients who had detailed information, all were given corticosteroids, and 3 received immunosuppressive drugs. Four of these patients had granulocytopenia (WBC less than 4,000 cells/mm<sup>3</sup>). Only 4 patients were given antifungal therapy before death. Amphotericin B was the most commonly used antifungal drug. Mortality rate depended on the degree of granulocytopenia, organs affected and the delay of treatment.

The immune status of the patient is compromised by both SLE and corticosteroid therapy. Corticosteroids and immunosuppressive drugs can suppress T and B cell functions, decrease cytokine production, inhibit recruitment of neutrophils and monocyte-macrophages to inflammatory sites, and decrease phagocytosis (11,12). These effects resulting in impaired neutrophils and macrophages function and favor aspergillus infection. The reason why aspergillosis does not occur more often in SLE patients is not known, but it might be related to epidemiological factors and the redundancy of the mechanism involved in defense against opportunistic pathogens. Unlike aspergillosis in other conditions, granulocytopenia is uncommon in patients with SLE (10).

The diagnosis of invasive pulmonary aspergillosis is difficult. Most patients present with dyspnea, non-productive cough or hemoptysis. Radiographs of the chest show diffuse pulmonary infiltrates. Sputum cultures are not helpful as they are positive only in 9 percent of patients (13). The diagnostic yield increases with bronchoscopic alveolar lavage and lung biopsy (14). Therefore the high



**Fig. 2** A follow-up chest radiograph, showing increasing in infiltrations in the right middle and lower lungs. Infiltration at the left upper lung is also noted.



**Fig. 3** Lung necropsy showing branching septate hyphae, with approximately 45 degree angulation, of aspergillus infiltrating the lung tissues (objective x 20).

index of suspicion and proper diagnostic investigations are required. The presence of septate hyphae in stained smears of sputum in an SLE patient with compatible clinical features should alert the physician for invasive pulmonary aspergillosis. The ignorance of the sputum examination, the delay in the diagnosis and treatment could contribute to death in this patient.

In conclusion, invasive pulmonary aspergillosis in SLE is a rare but fatal infection. The diagnosis is often delayed or missed. Awareness of this condition with proper diagnosis and management could help to improve the outcome of the disease.

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