Published in final edited form as:

Am J Crit Care. 2013 September ; 22(5): 448–451. doi:10.4037/ajcc2013659.

Invasive Aspergillosis Masquerading as Catastrophic Antiphospholipid Syndrome

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Abstract

A 25-year-old woman with a history of systemic lupus erythematosus who was taking steroids came to the hospital because of vague signs and symptoms of weight loss, constipation, and oral ulcers. Multiorgan dysfunction developed, and catastrophic antiphospholipid syndrome was suspected. She was treated with an intravenous infusion of heparin, but she experienced a subdural hemorrhage and died on day 10 of the hospitalization. An autopsy revealed disseminated invasive aspergillosis. This case illustrates that invasive aspergillosis is a frequently missed diagnosis and should be part of the differential diagnosis for any patient who is immunosuppressed, including patients with autoimmune diseases such as systemic lupus erythematosus.

When patients with systemic lupus erythematosus (SLE) are critically ill, the differential diagnosis often includes worsening of the underlying rheumatological disease, infection, and thrombosis. Because therapy for each of these possibilities can be harmful if the initial diagnosis is incorrect, treating these patients is especially challenging.

Case Description

A 25-year-old woman with a 2-year history of SLE treated with hydroxychloroquine 200 mg and prednisone 5 mg daily went to a hospital after 3 weeks of weight loss, constipation,

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FINANCIAL DISCLOSURES

Financial support was provided by NIH/NIA P30 AG-028747 (Dr Verceles).

weakness, myalgias, oral ulcers, and the inability to maintain adequate nutritional intake. She said that she had not traveled recently, had not had any contact with anyone who was sick, and had not experienced any bleeding or clotting disorders. In the initial days of hospitalization, she had renal failure, acute pancreatitis, and a transaminitis that could not be diagnosed with certainty. After a witnessed tonic-clonic seizure and respiratory arrest requiring intubation, she was transferred to the intensive care unit at a tertiary care hospital for further management.

Treatment was started with empiric antibiotics, antiepileptics, and heparin for the presumptive diagnosis of lupus cerebritis and suspected catastrophic antiphospholipid syndrome. Additionally, the patient had plasmapheresis and administration of pulse-dose steroids and intravenous immunoglobulin, and her condition improved during 3 days of treatment. Unexpectedly, a laboratory assay revealed that she had no antiphospholipid antibodies. On hospital day 7, a subdural hemorrhage and refractory acidosis developed. Treatment with antimicrobials was restarted, including administration of amphotericin B for possible fungal infection. Despite these interventions, worsening multiorgan dysfunction developed. After several days, the patient became unresponsive, with worsening shock requiring maximal doses of multiple vasopressor agents. Because of the deterioration in her condition despite maximal support, her family elected to start palliative measures, and comfort care was provided. The patient subsequently died on hospital day 10.

When the patient was admitted to the intensive care unit, she was afebrile, receiving mechanical ventilation with a 50% fraction of inspired oxygen, tachycardic, and had vasopressor-dependent shock. White oropharyngeal plaques were present on her hard palate and the posterior part of the pharynx, and healing scabs covered her upper and lower lips. Bilateral necrosis of the fingertips indicated peripheral ischemia. Laboratory data were white blood cell count 8000/ μ L, partial thromboplastin time 79 seconds, prothrombin time 22.8 seconds, international normalized ratio 1.9, and no bacterial or fungal growth on cultures of blood, sputum, and urine. Initial computed tomography of the chest, abdomen, and pelvis revealed a segmental pulmonary embolism in the right upper lobe, moderate bilateral pleural effusions, and bilateral renal and splenic infarcts.

The autopsy revealed disseminated *Aspergillus fumigatus* with invasion of the blood vessels, resulting in thrombosis and hemorrhage in the brain, lungs, myocardium, liver, pancreas, and kidneys (Figure 1). Histopathological examination showed invasive aspergillosis with fungal elements invading the lungs, brain, and blood vessels (Figure 2).

Discussion

Differential diagnosis in patients with SLE who are critically ill may overlap multiple organ systems. Thus, these patients are particularly challenging to manage, because potentially life-saving therapies can have markedly harmful sequelae.

Invasive aspergillosis is a life-threatening infection that most often occurs in patients with prolonged neutropenia associated with malignant hematological neoplasms, bone marrow transplants, solid organ transplants, and burns.¹ Among instances of invasive aspergillosis,

invasive pulmonary disease accounts for 50% to 60%; approximately 20% are disseminated disease.¹ The diagnosis of invasive aspergillosis is difficult because 30% to 50% of patients have no evidence of the fungus on blood and sputum cultures.²

Of note, infections are responsible for 20% to 55% of all deaths in patients with SLE.^{2,3} SLE itself results in an immunosuppressed state through aberrations in normal immune defenses. In addition, immunosuppressive agents used to treat autoimmune disorders such as SLE result in further immunosuppression, increasing susceptibility to fungal infections.

Diagnosing invasive aspergillosis is a major challenge. The difficulty of obtaining proper samples and the poor results of cultures for microbial growth make acquisition of objective evidence a problem. Because of the widespread presence of *Aspergillus* in the environment, aspergillosis can be diagnosed only on the basis of the results of blood or urine cultures or histological examination. Consequently, in critically ill patients, results of sputum cultures or samples collected by bronchoalveolar lavage in conjunction with radiographic evidence are often sufficient for starting empiric treatment. Only a few studies^{4,5} have been published on the diagnosis of invasive aspergillosis based on imaging. The investigators^{4,5} focused on patients with febrile neutropenia, and generalization of the findings to patients with SLE is questionable.

Galactomannan, a polysaccharide component of the *Aspergillus* cell wall, is a marker that may be useful in diagnosing invasive aspergillosis. The test for the polysaccharide can be performed on most biological specimens and has a sensitivity of 90% and a specificity of 98% for diagnosis of invasive aspergillosis.⁶ However, the presence of detectable serum levels of galactomannan preceded radiographic changes by a week in most patients, and the study included only patients with hematological malignant neoplasms and stem cell transplants.⁶

Management

Less controversy surrounds the treatment of invasive aspergillosis and disseminated aspergillosis. Mortality due to invasive aspergillosis without treatment is close to 100%,¹ partly because of the underlying autoimmune or immunosuppressed state of the infected patients. The optimal timing of treatment could not be determined in prospective studies, but the consensus is that starting empiric systemic antifungal treatment at first sign of infection yields the highest survival rate.¹ The gold standard of systemic antifungal treatment is voriconazole, although liposomal amphotericin B seems to be a suitable alternative.⁷ Combination therapy with 2 antifungal agents with different mechanisms of action may be a promising strategy,⁸ although randomized, controlled clinical trials of such therapy have not been done. In fact, the combination of a triazole with amphotericin B may be antagonistic.⁹ In patients with pulmonary hemorrhage, surgical resection of lesions adjacent to large blood vessels may reduce the recurrence of aspergillosis in patients anticipated to undergo future episodes of severe immunosuppression.¹⁰

Because of the multisystem involvement and the difficulty in confirming fungal infections, a diagnosis of invasive aspergillosis should always be considered in patients who are immunocompromised, such as those with SLE, whether or not the patients are receiving

immunosuppressive therapy. Early, empiric therapy with antifungal agents should be considered in patients with SLE who are critically ill.

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Figure 1.

Gross pathological findings in a patient with systemic lupus erythematosus and invasive aspergillosis. A, Petechial hemorrhage of the heart. B, Frank hemorrhage of the serosal surface of all 5 lobes of the lungs.

Figure 2.

Hematoxylin and eosin staining of tissue samples obtained at autopsy from a patient with systemic lupus erythematosus and invasive aspergillosis. Arrows indicate classic acute angle (45°) branching pattern of *Aspergillus fumigatus*. A, *A. fumigatus* invading the blood vessels in the lung, leading to total destruction and extravasation of red blood cells into the surrounding tissue. B, Negative images of *A. fumigatus* in the wall of an intact meningeal blood vessel.