

# Invasive Aspergillosis Diagnosed by Fine-Needle Aspiration of the Thyroid Gland

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## ABSTRACT

Invasive aspergillosis has been increasingly recognized as causing significant morbidity and mortality in immunocompromised patients but has never been diagnosed by fine-needle thyroid aspiration. A 24-year-old female with systemic lupus erythematosus presented with cough, shortness of breath, and fever of unknown origin unresponsive to broad-spectrum antibiotics. History and physical examination failed to indicate a source of infection. An  $^{111}\text{In}$  white blood cell scan showed thyroid localization. Physical examination revealed a multinodular goiter with a left dominant nodule. Fine-needle aspiration biopsy of a thyroid nodule revealed branching hyphae suggestive of *Aspergillus* sp. Despite immediate and aggressive treatment with amphotericin B and fluconazole, the patient died of overwhelming infection.

## INTRODUCTION

INFECTION IS THE MAJOR CAUSE OF MORBIDITY and mortality in systemic lupus erythematosus (SLE). Invasive aspergillosis has been reported in 23 patients with SLE (1,2). Risk factors for acquiring aspergillosis in these patients were high-grade disease activity, granulocytopenia, use of steroids, and other immunosuppressive treatment or antibiotic therapy for bacterial infection. Pulmonary disease (pneumonia or lung abscess) is the most common presentation of invasive aspergillosis, the brain being the most common site of extrapulmonary spread (3). Infiltration of the thyroid gland can occur and at least 26 cases of thyroidal infection caused by *Aspergillus* species have been reported in the world literature (4,5). All of the affected patients were immunocompromised; glucocorticoid therapy, leukemia, and lymphoma were the most common underlying conditions (6).

Aspergillosis presents a diagnostic as well as a therapeutic challenge. Few cases are recognized in life and the disease is more likely to be first diagnosed at necropsy (7,8). Twenty percent of autopsies of patients who died from disseminated aspergillosis showed involvement of the thyroid gland (9). Only a few cases were diagnosed antemortem, either by blood cultures (10) or transbronchial biopsy.

The present report describes a patient with active SLE who developed invasive aspergillosis. The diagnosis of disseminated fungal infection was made by fine-needle aspi-

ration of the thyroid gland. This is the first reported case of invasive aspergillosis diagnosed by fine-needle aspiration of the thyroid gland antemortem. Consistent with previous observations in cases of extrapulmonary spread, prognosis was poor and treatment was ineffective.

## CASE REPORT

A 24-year-old female with SLE since the age of 14, which was complicated by end-stage renal disease, presented to the University Hospital with complaints of fever (104°F), cough, and worsening shortness of breath.

The patient had been on long-term hemodialysis since 1995 and her disease had been in clinical remission until June 1998 when she developed an exacerbation after an episode of pharyngitis. Serologies showed elevated lupus antibodies with decreased complement levels. She was treated with increased doses of steroids and a single dose of 7.5 mg methotrexate with slight improvement. Two weeks after methotrexate, the patient developed pancytopenia secondary to bone marrow suppression resulting from methotrexate toxicity. She improved with treatment but 2 weeks later was admitted with the previously mentioned complaints.

Physical examination revealed a cachectic, febrile young female with temperature of 104°F, blood pressure of 152/84 mm Hg, and pulse of 110 beats per minute. She

had a prominent malar rash and alopecia. Jugular venous pressure was elevated. Lungs revealed bibasilar crackles and wheezes. On cardiac examination, a grade 3/6 systolic and diastolic murmur could be heard radiating to the apex, axilla and carotid areas. She had an arteriovenous fistula in the left arm. Neurological examination was normal.

Laboratory studies revealed a white blood cell count of 48,400/mm<sup>3</sup>, hematocrit was 23%, platelet count was 292,000. Blood urea nitrogen was 53 mg/dL and creatinine 9.6 mg/dL. Chest x-ray revealed bilateral infiltrates and cardiomegaly. She was empirically treated with ceftriaxone and azithromycin for pneumonia. Her hospital course was complicated by pericardial tamponade and acute pulmonary edema requiring brief intubation and artificial ventilation.

She remained highly febrile despite completion of a 2-week course of antibiotics. All cultures were negative. A white blood cell (WBC) scan, performed to determine the source of infection, showed increased accumulation of <sup>111</sup>I oxine labeled WBC in the thyroid gland and faint uptake in the left eye. The endocrinology service was consulted, and a multinodular goiter with a left thyroid nodule 2 × 2 cm was detected on examination. She denied any history of neck pain.

Thyroid function tests revealed thyrotropin (TSH) less than 0.03 μU/mL (0.4–4.0) and free thyroxine (FT<sub>4</sub>) 2.33 μU/dL (0.71–1.85) consistent with thyrotoxicosis and presumably due to thyroiditis. Fine-needle aspiration biopsy of the thyroid nodule revealed +1 branching gram-positive rods and abundant neutrophils admixed with a fungal organism consistent with *Aspergillus* (Fig. 1). Fungal cultures of the aspirate 28 days later confirmed *Aspergillus* species; amphotericin B and fluconazole were begun. She later complained of blurring of vision and pain over the left eye. Ophthalmologic evaluation indicated an endogenous endophthalmitis. Vitreal Gram's stain and cultures did not grow any organism. The patient's temperature de-

creased and she was discharged home, continuing amphotericin B.

One week later, the patient again presented with temperature of 103°F. Repeat thyroid function showed serum TSH 2.35 μU/mL (0.4–4.0) and total thyroxine (T<sub>4</sub>) 4.46 μU/dL (5.5–12.3). Computed tomography (CT) scan of the orbit did not reveal any retro-orbital or periorbital abscess. CT of the head showed three ring-enhancing lesions in the parieto-occipital region that yielded *Aspergillus sp.* on stereotactic biopsy. The patient lost her vision and because of continued fever, diagnostic as well as therapeutic enucleation of the left eye was performed. Pathology revealed subacute suppurative and granulomatous fungal endophthalmitis. The course of her illness was complicated by obstructive hydrocephalus secondary to ruptured intracranial abscess and bilateral iliac embolism that resulted from mitral valve fungal endocarditis. She underwent bilateral iliac embolectomy and mitral valve replacement. There were some signs of improvement; however, during a subsequent dialysis session the patient developed a generalized seizure and became unresponsive. A repeat CT of the head revealed left insular hemorrhage. She never regained consciousness and expired on the 59th hospital day.

Postmortem examination performed 12 hours after death revealed disseminated aspergillosis involving the heart and vegetative endocarditis of the mitral valve prosthesis. The left lung showed focal areas of necrosis with multiple vessels occluded by thrombi containing fungal hyphae; both lungs showed extensive acute pneumonia with pulmonary edema. The thyroid gland had multiple aspergillus-filled cysts. The spleen showed extensive necrosis with multiple infarcts. The kidneys showed end-stage disease. Examination of the brain revealed intracranial and intraparenchymal hemorrhage, 2.2 cm in greatest diameter, located in the left insular cortex with uncal herniation. Sections of the left middle cerebral artery revealed erosion of the arterial wall by *Aspergillus sp.* (confirmed by



FIG. 1. Aspirate smear of the thyroid nodule illustrating hyphal forms of *Aspergillus* species in a background of neutrophils. The individual hyphae are uniform, have parallel walls, show dichotomous 45° branching, and septation (oil immersion, GMS stain).

trichrome stain). Microabscesses were seen throughout the brain.

## DISCUSSION

In this report, we describe for the first time the successful diagnosis of invasive aspergillosis using fine-needle aspiration of the thyroid. Disseminated aspergillosis is one of the most common complications in patients with impaired host defense mechanisms. The symptoms and signs are nonspecific and overlap with other infectious and non-infectious processes. Because invasive *Aspergillus* infections are usually acquired by inhalation of *Aspergillus conidia*, pulmonary complaints predominate and include nonproductive cough, pleuritic chest pain, dyspnea, and fever. Fever unresponsive to broad-spectrum antibiotics is the earliest and most common sign of invasive fungal infection (3). Corticosteroids may camouflage the signs and minimize the symptoms. Particularly difficult to diagnose is the presence of fungal infections in patients with SLE. Often, the diagnosis and treatment is delayed because the multi-system disease caused by the organism may mimic SLE. The identification of bacterial infection might account for most of the clinical manifestations and discourage additional invasive diagnostic efforts that could demonstrate aspergillosis.

The clinical features of our patient were similar to those reported previously (1,2). She developed aspergillosis while she had active SLE that was being treated with high-dose steroids and cytotoxic agents. The time of entry of *Aspergillus* infection and the precise time course of dissemination in this case remain unknown. It is of interest that the first organ that led to the diagnosis of disseminated fungal infection was the thyroid gland. A 2 × 2 cm thyroid nodule on the left lobe was palpated and subsequent aspiration revealed fungal hyphae. Although asymptomatic with her thyroiditis, the patient had chemical evidence of thyrotoxicosis with elevated FT<sub>4</sub> and suppressed TSH. This is unusual, because thyroid function is unaltered in most cases of infectious thyroiditis and when abnormalities are present, hypothyroidism prevails. This transient phase of hyperthyroidism occurs after the release of excess thyroid hormones during the destructive phase of acute thyroiditis. The normalization of the patient's thyroid function test 2 weeks later is compatible with the natural course of thyroiditis. Whether this signifies improvement or worsening of the fungal infiltration of the gland is difficult to determine based on her thyroid function tests in such a short period of time.

Fungal infection of the thyroid gland is rare. In one report, 31 cases of fungal thyroiditis were identified, 26 cases were due to *Aspergillus* species, three to *Coccidioides immitis*, one to *Candida* and one to *Allescheria boydii* (4). *Aspergillus* is thought to infect the thyroid gland hematogenously, perhaps as emboli originating from infected pulmonary veins (6). Most lesions in the thyroid gland were described as focal abscesses, patchy hemorrhagic lesions due to vascular invasion or diffuse necrotizing thyroiditis (5).

Antemortem diagnosis of invasive aspergillosis is often not made because *Aspergillus* organisms are difficult to iso-

late and culture. Growth of *Aspergillus* in blood cultures is rare but highly specific (10). Infiltrates seen on chest x-ray are often read as pneumonia. In a study done by Boon et al. (12), 32 cases of aspergillosis were identified out of 2315 necropsies. Thirty cases had chest x-rays and 23 were read as pneumonia, 5 had nonspecific changes (edema or effusion), and only 2 had radiological evidence of possible fungal infection. <sup>111</sup>I WBC scans are sometimes done in cases of fever of unknown origin. Suppurative thyroiditis diagnosed in <sup>111</sup>I WBC scan has been previously reported (11). Antigen detection assays have been used with a sensitivity of 16%–95% (8). However, a majority of the cases were identified at necropsy (7–9,11,12).

We report the first case of disseminated aspergillosis involving the thyroid gland, diagnosed by antemortem fine-needle aspiration, and subsequently confirmed by cultures from the specimen obtained. The results of the fine-needle aspiration allowed for the appropriate treatment to be instituted.

Not only is the diagnosis a challenge but treatment is as well. An unacceptable high mortality rate from invasive aspergillosis of 50% or more is still found. Contributing factors to this poor outcome are the resistance of the aspergilli to most available antifungal agents, inadequate pharmacological properties or toxic side effects of these drugs, and frequent delays in the initiation of systemic antifungal treatment. It has been shown in previous studies that prognosis is worse once extrapulmonary spread of aspergillosis has occurred and treatment is usually ineffective.

In summary, systemic aspergillosis is a life-threatening complication of active SLE. Unfortunately, clinical, radiological and microbiological as well as serological diagnoses remain unreliable. The thyroid is a relatively common site of dissemination in aspergillosis and should arouse suspicion in patients at risk for fungal infection who have local thyroid findings. Fine-needle aspiration of the thyroid should be performed more frequently in these patients to aid in establishing this difficult diagnosis.

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