an echo which follows a pause. This is because the echo is relatively premature after a cycle of 110, when compared with its occurrence after a long pause of 200. It consequently is associated with slower retrograde or antegrade conduction (or both) due to incomplete recovery. When cycle II is 106 or less, the ensuing echo is completely blocked both retrogradely and antegradely. Such an echo would consequently not reach or reset the sinus node and would also not reach or depolarize the atria (illustrated by the dashed lines in the top strip, diagram B, of Fig 3).

The arrhythmia disappeared after the serum levels of potassium were lowered by hemodialysis. It is thus clear that the hyperkalemia played a significant role in the genesis of the sinoatrial block. The hyperkalemia not only precipitated the sinoatrial block, but also facilitated the occurrence of the sinoatrial echoes by slowing sinoatrial conduction.

References
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Invasive Pulmonary Aspergillosis Complicating Influenza A Pneumonia in a Previously Healthy Patient*


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A rare occurrence of invasive pulmonary aspergillosis complicates influenza pneumonia in a previously healthy adult. Five other similar cases are reported in the literature. Both transient depression of cell-mediated immunity and loss of ciliary function in the tracheobronchial tree occurs during acute influenza illness and may predispose to fungal superinfection. Early diagnosis and treatment of opportunistic Aspergillus infection complicating influenza is mandatory in view of the high mortality associated with this complication.

Invasive aspergillosis is an uncommon condition complicating predominantly immunocompromised patients. Its occurrence complicating influenza in previously healthy patients has only rarely been documented. We report the case of a previously well 28-year-old woman who developed fatal invasive aspergillosis following influenza A pneumonia. We review the existing literature and comment on the pathogenesis of this serious complication.

Case Report

A 28-year-old previously healthy student actress was admitted to the respiratory intensive care unit of the Johannesburg Hospital following respiratory arrest. An orotracheal tube was inserted, and the patient was mechanically ventilated.

There had been a week-long history of a viral-type illness characterized by malaise, chills, fever, myalgia, rhinorrhea, and sore throat. For two days prior to admission, the patient had complained of progressive dyspnea and a productive cough.

Physical examination revealed rectal temperature of 39°C and pharyngitis. Her pulse rate was 130 beats per minute with recurrent short runs of ventricular tachycardia. Examination of the heart revealed no cardiomegaly, but a left atrial gallop was noted. Diffuse bilateral crackles were audible on auscultation of the chest.

Large volumes of tenacious reddish brown secretions were suctioned from the endotracheal tube during the first 24 hours. On one occasion soon after admission, reinsertion of the trachea was
The chest roentgenogram on admission showed patchy bilateral opacification at both mid zones and lower zones. The ECG showed diffuse T wave inversion and intermittent runs of ventricular tachycardia.

Pertinent laboratory values included the following: a hemoglobin of 11.5 g/dl; white blood cell count of 19,400/cu mm (86 percent neutrophils, 8 percent lymphocytes, 6 percent eosinophils); and platelets of 178,000/cu mm. Arterial blood gas values were obtained only after the institution of mechanical ventilation which revealed a PaO$_2$ of 65 mm Hg and PaCO$_2$ of 30.3 mm Hg (FiO$_2$, 0.5; PEEP, 5 cm H$_2$O).

Sputum microscopy on admission revealed hyphae and mycelia of Aspergillus which was documented on numerous subsequent specimens. Florid cultures of Aspergillus fumigatus were obtained from the sputum. No eosinophils were noted in the sputum and Aspergillus precipitins were negative. An Aspergillus skin test (using highly purified antigen prepared by the South African Institute of Medical Research) was negative at 20 minutes, after six to eight hours, and after 72 hours. Skin tests for PPD, Candida, streptokinase, and streptodornase were also negative. Other immunologic studies revealed increased numbers of T suppressor cells, but normal levels of T helper cells (T helper:T suppressor = 1:4). Quantitative levels of immunoglobulins (IgG, IgM, IgA) were normal as was total hemolytic complement, C3 and C4.

Viral serology on admission (utilizing a complement fixation test) revealed a titer of 1/64 to influenza A. This rose to a titer of 1/256 some ten days later. Other extensive microbiologic studies yielded negative results. In particular, direct fluorescent antibody staining of sputa for Legionella organisms and serial indirect fluorescent antibody studies for Legionella were negative. Serial complement fixation tests for Mycoplasma organisms were also negative.

Initial specific therapy consisted of intravenous penicillin, tobramycin, and erythromycin. As the patient was rapidly deteriorating on admission, hydrocortisone (200 mg, six hourly) was added to the treatment regimen. This was administered intravenously for six days, the dose being progressively reduced over this period. The patient failed to improve clinically, and serial chest roentgenograms showed a progressive increase in consolidation bilaterally. On the tenth hospital day, large areas of cavitation were noted in the left upper and lower lobes and the right upper lobe (Fig 1). Tranbronchial biopsies performed at this time showed evidence of a necrotizing pneumonia and focal invasive aspergillosis. Amphotericin B was then administered to the patient, and a total of 170 mg was given over the following six days. Her condition, however, steadily worsened, and she died on the 16th hospital day.

Histologic sections of the lungs at postmortem showed extensive areas of organizing pneumonia with multiple foci of abscess formation. Extensive infiltration by fungi of the Aspergillus species was noted (Fig 2). In addition, most of the segmental bronchi showed denudation of the mucosa and replacement by proliferating epithelial cells showing squamous metaplasia (Fig 3). These features are highly suggestive of a fulminating influenza necrotizing bronchitis. The lumina of the bronchi were filled with necrotic debris with

### Table 1—Invasive Aspergillosis Associated with Influenza

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Abbott et al$^2$</th>
<th>Fisher and Walker$^3$</th>
<th>Fisher and Walker$^3$</th>
<th>Jarwalla et al$^4$</th>
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<td>A</td>
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*NS = Not stated

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**Figure 2.** Lung parenchyma showing invasive aspergillosis (Grocott stain, original magnification × 750).

**Figure 3.** Regenerative changes in bronchus showing bronchial squamous metaplasia (hemotoxylin-eosin, original magnification × 300).
numerous polymorphs which extended into the alveolar spaces. The alveoli showed evidence of acute cellular injury. A section of myocardium showed focal abscesses in which Aspergillus hyphae were present.

DISCUSSION

The occurrence of invasive pulmonary aspergillosis complicating influenza in previously healthy patients has been reported in only five patients, the details of which, together with our case, are summarized in Table 1. The mean age of the six patients (all women) was 44.7 years (range: 14 to 69 years). Four of the patients were smokers. Lymphopenia of varying degree was present in all the previously reported cases and was borderline low in our patient. In those patients in whom skin tests were reported, cutaneous anergy was uniformly present. Broad spectrum antibiotics had been administered to five of the six patients and corticosteroids to two patients. Viral serology was positive for influenza A in four patients and parainfluenza in one. Despite the fact that the clinical picture together with various investigations (sputum microscopy and culture, tracheal aspirate, serum precipitins, lung biopsy) either suggested or confirmed the presence of invasive aspergillosis in five of the six patients, only two of the patients were treated with antifungal drugs (amphotericin B or fluconazole), and all but one patient died (83.3 percent mortality).

There are a number of pathogenetic mechanisms whereby influenza may predispose to fungal superinfection. Influenza A virus usually attacks the columnar ciliated respiratory epithelium of the airways with resultant necrosis. These changes may extend down to the level of the terminal bronchioles and alveoli. Regenerative changes begin after about five days with proliferation of typical basal cells to form a nonciliated squamous metaplastic type of epithelium, a typical histologic feature of influenza pneumonia (Fig 3). Thus, the airways during the early stages of influenza pneumonia are devoid of ciliary lung defenses and may be prone to attack by secondary invaders, bacterial being most commonly reported.

Suppression of cell-mediated immunity during influenza illness has been well documented. This has been characterized by cutaneous anergy and diminished lymphocyte stimulation by phytohemagglutinin. Diminished cell mediated immunity, as may occur following influenza, measles, or cytomegalovirus infections, may be complicated by opportunistic fungal infections. It is of interest that T suppressor/cytotoxic cell augmentation such as occurred in our case has been reported in both the acute and convalescent stages of a number of viral infections including Epstein-Barr, cytomegalovirus, and varicella. In our case, the normal levels of T helper cells, the T helper: T suppressor ratio > 1.0, and normal levels of immunoglobulins would argue strongly against a diagnosis of the acquired immunodeficiency syndrome (AIDS) as a marked reduction in T helper cells, with a T helper: T suppressor ratio commonly ≤ 0.5 and increased levels of immunoglobulins are characteristic of that condition associated with opportunistic infections. It has been suggested that the elevation of T suppressor/cytotoxic cells following viral infections may constitute a normal immunologic response to that infection.

Both corticosteroids, which depress T lymphocyte function, and prolonged broad spectrum antibiotics have been implicated in the development of fungal superinfection. In previously healthy asthmatic patients, corticosteroids were implicated in the development of invasive pulmonary aspergillosis, and broad spectrum antibiotics have been cited in the pathogenesis of Aspergillus superinfections. In our patient, and in some of the previously reported cases, these drugs almost certainly aggravated the course of the Aspergillus infection and may well have had a pathogenetic role in its genesis.

As acute influenza illness may predispose to infective complications including invasive pulmonary aspergillosis, it is important to take heed of positive sputum microscopy and cultures for Aspergillus in this setting and to follow on with appropriate diagnostic procedures. Early diagnosis and treatment is mandatory if one is to effect a cure in this rapidly fatal complication of influenza disease.

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