

Invasive pulmonary aspergillosis in a non-immunosuppressed patient: successful management with systemic amphotericin and flucytosine and inhaled amphotericin

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Invasive pulmonary aspergillosis is an increasingly recognised condition, occurring almost exclusively in severely immunocompromised patients.¹ Fewer than 30 cases of invasive pulmonary aspergillosis have been described in apparently immunocompetent hosts; most of these patients had one or more possible risk factors, such as fibrotic lung disease,² use of corticosteroids,³ recent influenza or psittacosis infection,⁴ and possibly alcoholism. The prognosis of invasive pulmonary aspergillosis is dismal in both immunosuppressed and immunocompetent patients. We report a non-immunosuppressed patient who was apparently cured after systemic treatment with amphotericin and flucytosine, together with inhalations of aerosolised amphotericin.

Case report

A 48 year old welder was admitted to the intensive treatment unit in December 1982 because of pneumonia with impending respiratory failure. He had been in good health until 1980, when he was admitted to hospital because of a severe attack of asthma. Allergy to several inhalation antigens was established, with an appreciably raised total IgE level of 8500 U/l (normal <390 U/l). Skin tests using an *Aspergillus fumigatus* extract yielded negative responses, but the RAST test for IgE antibodies against *A fumigatus* was positive and a double diffusion test for IgG antibodies against *A fumigatus* showed three precipitation arcs. The patient was discharged taking thiazinamium, cromoglycate and beclomethasone inhalations. During the subsequent two years he was well but he drank alcohol to excess.

Several days before admission he had developed a non-productive cough with dyspnoea and wheezing. Because of concomitant alcohol intoxication his memory was only fragmentary. On admission he was cyanosed and obtunded with pyrexia of 40.4°C. The chest radiograph showed an opacity in the left lower lobe. The white blood count was $9.3 \times 10^9/l$ with a normal differential count. Microscopic examination of a sputum sample showed no pathogens and treatment was started with cefuroxime, corticosteroids, and theophylline. During the next few days the patient's condition rapidly improved, the fever abated, and the chest radiograph showed progressive clearing of the infiltrate.

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On bronchoscopic examination no abnormalities were noted and cultures were negative. Cytological examination of the brushings obtained at bronchoscopy showed branching septate hyphae consistent with *A fumigatus*, but these findings were considered of no clinical significance.

On the 19th hospital day the fever recurred and the patient felt weak. Tobramycin was added to the regimen with no improvement. Therapeutic trials with erythromycin and co-trimoxazole were also ineffective. The patient's condition gradually deteriorated and the chest radiograph showed patchy infiltration in both lung fields, with a large cavitating mass in the left upper lobe (fig). Tomography showed several cavities, some with air-fluid levels. All antibiotics were discontinued and on the 36th hospital day a percutaneous lung biopsy specimen was obtained. Pathological examination showed necrotic lung parenchyma with a dense polymorph infiltration containing many eosinophils. Cultures yielded abundant growth of *A fumigatus*; no other microorganisms were found.

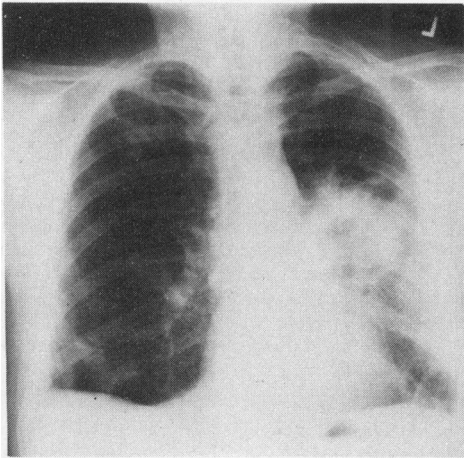
On the 41st hospital day antimycotic treatment was started, consisting of oral flucytosine 150 mg/kg daily and amphotericin increasing to 50 mg intravenously per day. Amphotericin was also given by inhalation together with 3 ml of 5% dextrose in a model 1720 "up draft" nebuliser (Hudson, Temecula, California). The aerosol was inhaled four times daily. The starting dose was 5 mg/day and was doubled daily until a dose of 100 mg/day was reached.

The patient remained afebrile and the chest radiograph slowly improved, with a residual cavity in the left upper lobe. Because of hypokalaemia the intravenous amphotericin dose was decreased after two weeks to 50 mg on alternate days. Antimycotic treatment was stopped

Serological data on the patient

Time (w) to ad- mission	CFA titre		ELISA*	Double diffusion†	Specific IgE‡ (U/ml)
	Influenza A	Psittacosis			
-52				0	2-5
0	1/8	1/64		0	0
2	1/8	1/64 (IgM+)	0	0	0
4	1/64	1/128	+	4	2-5
6	1/128	1/128	++	4	5-10
9	1/16	1/128	++	8	2-5

*Anti-*Aspergillus* antibodies (IgG) determined by ELISA.¹⁰ †Anti-*Aspergillus* antibodies (IgG)-number of precipitation arcs by double diffusion technique. ‡Specific IgE anti-*Aspergillus* antibodies (RAST). CFA—complement fixing antibodies.



Chest radiograph, showing densities in both lung fields and a large cavitating lesion in the left upper lobe.

after eight weeks at a cumulative intravenous dose of amphotericin of 1725 mg.

The result of serological studies are shown in the table. In addition to the antibodies to *A fumigatus* there was serological evidence of a recent infection with influenza A virus. The cause of the raised titre of *Chlamydia psittaci* antibodies is not known but a recent venereal infection would be a possible explanation.

Discussion

The treatment of choice is probably a combination of amphotericin and flucytosine,⁵ as these two drugs act synergistically against *Aspergillus* spp and other fungi.⁶

The bronchial tree and cavities communicating with the airways constitute an important sanctuary for the fungus if systemic treatment only is used. In contrast to flucytosine, systemically administered amphotericin enters bronchial secretions in minimal concentration or not at all.⁷ The combination therefore effectively acts as a single agent locally, which is undesirable since flucytosine is known to rapidly induce fungal resistance if used alone. Inhalation treatment with amphotericin may help to eradicate the

fungus in the bronchial tree and prevent continuing reinfection with flucytosine resistant strains.

Only a small proportion of the inhaled agent may be expected to reach the microorganism since it is usually located in poorly ventilated parts of the lung. It is therefore of considerable importance that the non-absorbable amphotericin can be inhaled in doses much larger than can be used in systemic treatment. Although the safety and convenience of inhalation of amphotericin B aerosols have been documented,^{8,9} we have not been able to find any previous reports of this treatment in invasive pulmonary aspergillosis. Further study is needed to define its role in the management of this serious infection.

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