Case Report

Cavitating Cryptococcal Pneumonia in the Immunocompetent Host

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Abstract

Introduction: Isolated cryptococcal pneumonia in the immunocompetent host is a rare infection. Indications for treatment and its duration are currently not defined. Clinical Picture: Three patients presented with cavitating cryptococcal pneumonia. Treatment: They were treated with oral fluconazole. Outcome: Improvement was evident clinically, radiologically and serologically. Fluconazole was continued until serum cryptococcal antigen (SCA) levels were negative in our patients as they had manifestations such as haemoptysis, cavitating or multi-lobar pneumonia and relatively high antigen levels, suggesting potentially serious disease. Conclusions: Fluconazole is effective and safe for the treatment of cryptococcal pneumonia in the immunocompetent host. Although the role of monitoring SCA levels in the immunocompetent host is currently unclear, it may be an indication of infective burden and the benefits of longer treatment seem to outweigh the risks.

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Key words: Antifungal therapy, Cryptococcal antigen, Cryptococcosis, Duration, Fluconazole, Haemoptysis, Serum cryptococcal antigen

Case Reports

Three immunocompetent male patients with cryptococcal pneumonia presented to our hospital between June 2000 and November 2001. They had varied presentations, as shown in Table 1. All 3 patients were previously well, without any underlying diabetes mellitus, renal or hepatic diseases, and none was on any immunosuppressants. None of them appeared Cushingnoid. Their blood counts, including differential counts, were normal. Two patients had normal CD4 and CD8 counts. They all tested negative for human immunodeficiency virus (HIV). Central nervous system (CNS) involvement was excluded by cerebrospinal fluid (CSF) analysis, which was negative for cryptococcal antigen and fungal culture. Two patients had known long-term exposure to pigeons around air-conditioning vents outside their workplace and areas of residence. The third patient had no such exposure.

Chest radiographs (CXRs) and computed tomogram (CT) of the thorax revealed lobar consolidation with cavities in all 3 patients (Figs. 1 and 2). Two patients had multi-lobar involvement.

All 3 patients initially received antibiotics as for community-acquired pneumonia, but showed no clinical improvement after 1 week. Subsequently, they underwent CT thorax, diagnostic bronchoscopy and bronchoalveolar lavage (BAL). Two patients underwent bronchoscopic lung biopsy (BLB) and histology was diagnostic of infection with cryptococcus. A BAL specimen grew *Cryptococcus neoformans* in the third patient. Serum cryptococcal antigen (SCA) levels were elevated in all 3 patients.

Table 2 shows the treatment and response to therapy. They were commenced on fluconazole 400 mg to 800 mg per day. Clinical improvement was the earliest to manifest followed by radiological resolution, and finally, seronegativity (Fig. 3). CXRs and SCA levels were monitored 6 to 8 weekly for response to therapy. Duration of therapy was between 5 months and 14 months. Potential side effects from fluconazole monitored included nausea, vomiting, diarrhoea and transaminitis. Liver function tests were monitored every 4 to 6 weekly and fluconazole was

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Table 1. Characteristics of Patients

Patient (Age, years)	Presenting symptoms	CXR findings	CT thorax findings	BAL results	BLB results	SCA
1 (41)	Cough, LOW for 6 weeks, haemoptysis for 1 day	RLL and LLL consolidation	RLL consolidation with cavities and LLL consolidation	Normal	RLL: Necrotising granulomatous inflammation, fungal yeast forms (mucicarmine-positive)	1:4
2 (46)	Dry cough and breathlessness for 3 weeks	RLL consolidation	RLL consolidation with cavities	Normal	RLL: necrotising granulomatous inflammation, fungal yeast forms (mucicarmine-positive)	>1:512
3 (30)	Cough with yellow sputum for 2 weeks	LUL cavities and bilateral UL consolidation	LUL cavities and bilateral UL consolidation	Fungal yeast forms. Culture-positive.	Not done	1:256

BAL: bronchoalveolar lavage; BLB: bronchoscopic lung biopsy; CT: computed tomogram; CXR: chest radiograph; LLL: left lower lobe; LUL: left upper lobe; LOW: loss of weight; RLL: right lower lobe; SCA: serum cryptococcal antigen; UL: upper lobe

Table 2. Treatment and Response

Patient	Treatment and duration	Duration of therapy to resolution or normalisation of:			Follow-up duration
		Symptoms	CXR	SCA	
1	Fluconazole 400 mg/day for 5 months	1 week	3 months	5 months	23 months
2	Fluconazole 400 mg/day for 14 months	2 weeks	7 months	14 months	22 months
3	Fluconazole 800 mg/day for 11 months	12 weeks	11 months	11 months	39 months

CXR: chest radiograph; SCA: serum cryptococcal antigen

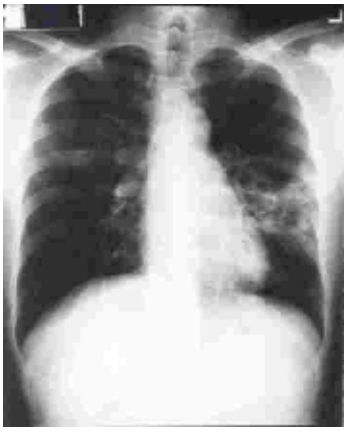

Fig. 1. Chest radiograph of the third patient at presentation. Bilateral upper lobe consolidation with left upper lobe cavities were present.

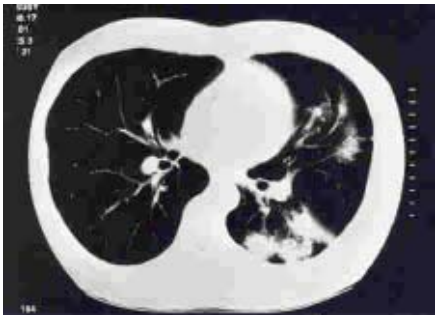

Fig. 2. Computed tomogram of the same patient showing nodular cavities in the left upper lobe.

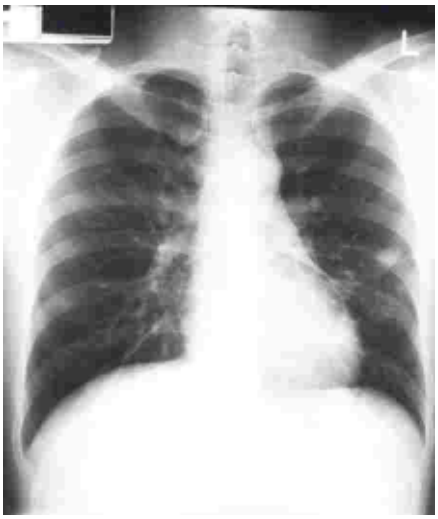

Fig. 3. Chest radiograph of the same patient, 11 months later, showing residual scarring in the left upper lobe.

well tolerated, without any side effects, in our patients. They did not have any signs and symptoms of dissemination nor relapse at a mean follow-up duration of 28 months.

Discussion

Cryptococcal pneumonia in the immunocompetent host is rare. Few case series have been published to date and data obtained have generally not been complete due to the retrospective nature of these reports.[1] Cryptococcosis is known to infect immunocompetent patients such as ours but the reason for their susceptibility is unclear. Exposure to pigeon excreta and inhalation of the cryptococcal yeasts within the excreta may have contributed to the infection in 2 of our patients.[2] Nonetheless, even though it is generally

thought that disease occurs after the organism is inhaled, a history of exposure to pigeons is not thought to be helpful.[3]

The indications for the treatment of isolated pulmonary cryptococcosis in the immunocompetent have been controversial. This, in part, is related to the toxicity of amphotericin B, and in part, to the observation that the rate of dissemination in the immunocompetent host was minimal compared to that in the immunocompromised host.[4] Before the era of azole therapy, this condition was thought to be self-limiting, with reports of spontaneous resolution, and risks of treatment with amphotericin B outweighed the potential benefit. However, dissemination of the infection has been well described even in immunocompetent hosts. In a landmark study by Kerkering et al,[4] dissemination occurred in 1 of 7 "normal" hosts. In Nadrous et al's series,[5] 14% of patients (6 out of 42 patients) were found to have disseminated disease. In another series, 24 of 35 immunocompetent patients had concomitant pulmonary and CNS disease; this was associated with a high mortality rate of 40% amongst these 24 patients.[6] Therefore, current data seem to suggest that dissemination occurs in the immunocompetent host and that the disease may be associated with potentially life-threatening complications.

Fluconazole has been shown to be effective for cryptococcal pneumonia in many series.[1,2] However, due to the rarity of the disease, incomplete data on the immune status of the patients included in previous series and a lack of controlled clinical trials, its duration of therapy is subject to much debate. This is particularly true in the treatment of immunocompetent patients. The Infectious Diseases Society of America 2000 guidelines[7] recommend 3 to 6 months of fluconazole for immunocompetent patients who are symptomatic with SCA titre >1:8. In Nunez et al's series[1] of 4 immunocompetent patients, 6 to 8 weeks of fluconazole was given without relapse on 2 to 3 years of follow-up. SCA levels were monitored but did not determine the duration of therapy in their series.[1] Therapy was stopped if there was clinical, radiologic and serologic improvement. Patients were given 4 to 12 weeks of fluconazole in other series but immunocompromised patients were included and thus the results cannot be extrapolated to immunocompetent hosts.[2] We elected to treat our patients till they reached seronegativity. This may be subject to criticism because of the lack of evidence but due to the potentially life-threatening clinical manifestations, high SCA levels and lack of conclusive data from the current literature, fluconazole was continued, with careful monitoring for adverse effects, which did not occur in any of our patients. The cost-benefit of prolonged treatment should ideally be verified in formal studies, but due to the rarity of the disease, this may not be achievable. There is generally a minimal role for surgery in cryptococcal pneumonia, except as part of a diagnostic work-up.

SCA is said to have a high sensitivity and specificity for cryptococcal disease but its role in guiding therapy for non-HIV patients has never been studied. SCA titre may be an indication of infective burden as a high titre of cryptococcal antigen in CSF is a poor prognostic factor in acquired immunodeficiency syndrome patients and cryptococcal meningitis. In addition, patients with disseminated disease were found to have higher antigen levels in Aberg et al's series.[8] In comparison to Nunez et al's series[1] of patients with SCA titres of 1:4, 1:2,1:64 and 1:16, 2 of our patients had much higher SCA levels (1:256 and >1:512) and all 3 patients in our series had cavitating pneumonias. Therefore, we believe that our patients represented the more severe spectrum of cryptococcal pneumonia in immunocompetent hosts.

Conclusion

Three patients with severe manifestations, including cavitation and relatively high SCA titres, were treated successfully with oral fluconazole. Therapy was guided by a combination of resolution of symptoms, radiological changes and antigen levels. Extended fluconazole therapy appeared to be relatively safe and effective in such patients.

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