

Fungal pneumonia, chronic respiratory diseases and glucocorticoids

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Invasive pulmonary aspergillosis (IPA) usually occurs in severely immunocompromised patients. The expanded use of glucocorticoids (GC) in clinical practice accounts for the increasing number of fungal infections reported in mildly or non-immunocompromised hosts. We report a series of 8 patients with fungal pneumonia in whom long term high dose GC treatment was the only risk factor for opportunistic infections. All patients except one had chronic underlying disorders (asthma, idiopathic fibrosis, chronic obstructive pulmonary disease, COPD). Seven patients were diagnosed with pulmonary aspergillosis. Etiological suspicion of fungal infection was obtained during lifetime in six cases and in one case was confirmed only in the post-mortem examination. In most cases bronchoscopic techniques allowed identification of the microorganism. However, delay in establishing the diagnosis (mean 20 days) precluded a prompt initiation of a specific treatment. The course of the fungal infection was ominous. All but one patient experienced progressive respiratory failure requiring ICU admission and mechanical ventilation support. Despite this, all of them died. The only survivor was a patient receiving early empirical antifungal treatment due to a high clinical suspicion of fungal infection. Based on the present and previous findings, antifungal treatment should be considered in chronic respiratory patients requiring high or repetitive doses of GC when there is clinical evidence of pneumonia and isolation of *Aspergillus* spp. from respiratory secretions.

Keywords *Aspergillus*, glucocorticoids, COPD, bronchoscopy

Introduction

Glucocorticoids (GC) exert a decisive influence in the innate immune function of resident alveolar macrophages and granulocytes, the two major immunoregulatory cells in host defenses against opportunistic and bacterial infections. As a consequence, it might be expected for patients receiving long-term-high doses of GC to have depressed resistance to a wide variety of infective agents [1]. Glucocorticoids undoubtedly favour infectious complications when administered in patients with clinical conditions causing severe immunosuppression [2]. Patients particularly at risk are those with bone marrow transplant or prolonged neutrope-

nia. In this sense, high cumulative doses of GC administered for prophylaxis or treatment of graft-versus-host-disease are associated with both risk of acquisition and poor outcome of invasive aspergillosis [3]. Patients with other immuno-defective conditions such as cancer, solid organ transplantations, haematologic disorders and different vasculitis are also at risk for invasive fungal infections when exogenous GC therapy is administered.

Reports of serious opportunistic pulmonary infections in patients with chronic lung diseases requiring permanent or repetitive doses of GC have been occasionally described. These include cases of bacterial sepsis, herpes simplex, *Pneumocystis jirovecii* or cytomegalovirus pneumonia [4]. Patients with chronic obstructive pulmonary disease (COPD) requiring GC seem to be at special risk for *Aspergillus* infections [5,6]. We present a series of patients with opportunistic

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infections in whom the only immunosuppressive condition was long term treatment with high doses of GC.

Setting

The patients selected in this observational study were part of an extended population of 33 patients on chronic long-term GC treatment for different underlying disorders who developed pulmonary infiltrates [7]. The exclusion of patients also treated with other immunosuppressive drugs (i.e. cytotoxic agents) allowed the identification of 9 patients treated exclusively with high doses of GC. Eight out of the 9 patients treated exclusively with GC had chronic pulmonary disorders and one had systemic sclerosis. In 8 patients the final diagnosis was fungal pneumonia (7 cases of *Aspergillus* spp. and one case of *Candida tropicalis*) and one had a multi-drug resistant *Pseudomona aeruginosa* pneumonia. Clinical characteristics, diagnosis and outcome of the 7 patients with *Aspergillus* pneumonia are described.

Results

Table 1 shows the clinical characteristics of the group of patients receiving long term GC treatment who developed fungal pneumonia. Glucocorticoids were given for the management of bronchospasm, chronic asthma or diffuse interstitial involvement of the lung. Only two patients were current smokers. Clinical presentation was characterized by fever, increased dyspnea, hemoptysis (in 2 cases) and the apparition of pulmonary infiltrates in the chest X-ray films. Neutrophil counts were within the normal range and no patient had renal failure or diabetes mellitus (two patients developed acute hyperglycaemia during admission). Five patients were already receiving antibiotic treatment (antibacterial) when pulmonary infiltrates were first detected. In all cases blood samples were drawn for culture, but all of them were negative. Circulating galactomannan antigen test was performed in three patients with negative results. A sample of spontaneous sputum was obtained in 5 patients, but only one of them was positive for *Aspergillus* spp. High-resolution computed tomography (CT) scan was performed in three patients but did not report conclusive data of fungal infection (i.e. no evidence of 'halo' sign or 'air crescent' sign). After identification of the pulmonary infiltrates, all patients were treated with broad-spectrum antibacterial drugs. All patients were admitted to the ICU due to progressive respiratory failure and seven required mechanical ventilation.

Table 1 Clinical characteristics and demographic data of the population evaluated ($n=7$)

Demographic data	
Age, years	68 ± 6
Male/female, n	5/2
Underlying diseases	
Pulmonary idiopathic fibrosis	1
Chronic asthma	2
COPD	2
Post-TBC residual lung scars	1
Systemic sclerosis	1
Former smoker, n (%)	6 (71%)
FVC (%)	68 ± 12
FEV ₁ (%)	50 ± 26
Duration of GC therapy, days	154 ± 90
Cumulative doses of GC, mg	2360 ± 950
Pulmonary infiltrates	
Duration of symptoms (days)	13 ± 9
Fever, n (%)	7 (100%)
Bilateral radiographic involvement, n (%)	3 (43%)
Radiographic pattern	
Alveolar	3 (43%)
Alveolo-interstitial	1 (14%)
Cavitation	2 (29%)
Interstitial	1 (14%)
Nosocomial acquisition, n (%)	5 (71%)
Neutrophils, count × 10 ⁹ cells/L	9600 ± 4800
Albumin, g/L	26 ± 5
PaO ₂ /FiO ₂ ratio at hospital admission	188 ± 73
APACHE II at ICU admission	22 ± 6
Delay in diagnosis, days	20 ± 13 (9–38)
ICU requirement, n (%)	7 (100%)
Mechanical ventilation requirement, n (%)	6 (86%)
Mortality, n (%)	6 (86%)

Data are presented as mean ± SD (range) unless otherwise indicated.

Fiberoptic bronchoscopy (FOB) was performed in 5 patients (in two patients it was considered too risky due to severe acute respiratory failure-cases 2 and 7). A failure to respond to empirical therapy or unrevealing microbiological data by means of non-invasive procedures was the indication to perform FOB. The diagnostic yield of the different bronchoscopic procedures was as follows: bronchial aspirate 5/5 (100%), bronchoalveolar lavage 1/2 (50%), protected telescoping catheter 4/5 (80%) and transbronchial biopsy 1/1 (100%). Table 2 shows the diagnostic yield of the different techniques employed. Diagnosis of fungal pneumonia was established during lifetime in 6 cases, and at post-mortem examination in the last one. In five cases, the infection was of nosocomial-acquisition. The mean delay in establishing the diagnosis of fungal pneumonia was 20 days (range: 9–38 days). *Aspergillus fumigatus* was the most common microorganism isolated (6 patients). Bacteria were also isolated in two patients: *Aspergillus fumigatus* plus *Pseudomona aeruginosa* plus

Table 2 Diagnostic yield of the different diagnostic techniques employed

Case age (y)/sex IPA classification	Radiographic patter	GMM Ag	Sputum	BAS	BAL	PSB	TBB	Necropsy
1 (72/ M) proven	Cavitation	–	Negative	A. fumigatus	–	–	A. fumigatus	–
2 (55/ M) proven	Interstitial	–	–	–	–	–	–	A. fumigatus
3 (70/ M) probable	Alveolar	–	Aspergillus	A. fumigatus	–	A. fumigatus	–	–
4 (71/ F) possible	Alveolointerstitial	–	Negative	–	Negative	A. fumigatus	–	–
5 (68/ M) probable	Alveolar	Negative	Negative	A. fumigatus	–	A. fumigatus	–	–
6 (73/ M) possible	Alveolar	Negative	–	E. coli + A. niger	–	–	–	–
7 (66/ F) probable	Cavitation	Negative	–	A. fumigatus + Pseudomona a. + Stenotrophomona m.	A. fumigatus + Pseudomona a. + Stenotrophomona m.	A. fumigatus + Pseudomona a.	–	–

GMM Ag: galactomannan antigen test (serum). BAS: bronchial aspirate; PSB: protected specimen brush; BAL: bronchoalveolar lavage. TBB: transbronchial biopsy.

Stenotrophomona maltophilia and *Aspergillus niger* plus *Escherichia coli*. Using criteria designed for IPA in immunocompromised patients [8], IPA was classified as proven ($n=2$), probable ($n=3$) and possible ($n=2$). In 6 patients (80%), antifungal treatment was given. Only one patient received empirical antifungal therapy with itraconazole and Amphotericin B after 48 h of evolution, (and previous to having microbiological evidence of fungi in respiratory secretions) due to the high clinical suspicion of a fungal aetiology. This patient was the only survivor of the present series. One patient was never treated with antifungal therapy (case 2). Crude mortality was 86% (6 out of 7 patients). Four patients died during the first 10 days. The mean duration of antifungal treatment was less than 7 days for the majority of patients. Five patients developed septic shock and the final cause of death was multiorgan failure in all of them. In all cases, an attempt to tapering the dose of steroids was done.

Discussion

The present series highlights the potential for fatal fungal lung infections, particularly IPA, in patients receiving GC as a unique factor of immunosuppression. The number of cases of fungal pneumonia in patients with long term treatment with GC has increased as the use of GC expands in clinical practice [9–11]. Certainly, the minimum required GC exposure to be at risk for fungal pneumonia is difficult to quantify. This difficulty is further complicated by the frequent comorbidities and additional risk factors for opportunistic infections in affected patients. Stuck *et al.*, by pooling data from 71 controlled clinical trials, evidenced that the rate of infections was not increased in patients given a daily dose lower than 10 mg/day or a cumulative dose of <700 mg of prednisone [12]. In a revision of autopsy-proven cases of opportunistic pneumonia in patients on chronic GC treatment, the overall mean prednisone equivalent dose at the time of admission was 34 ± 8 mg/d. In the hospital stay, the maximum daily dose of methylprednisolone varied from 60 mg/d to 1000 mg/d given for a mean of 26 days [13]. In the present series, the mean cumulative dose of GC largely exceeded these doses. Interestingly, four of the patients included were also receiving high doses of inhaled GC (mainly fluticasone with an average dose of 1000 mcg/day). Cases of IPA have been reported with high-potency inhaled GC [14] and this circumstance could have had some additional influence in the development of fungal infections in some of the referred patients.

It has been speculated that patients with COPD are particularly at risk for developing fungal pneumonia when receiving high or repetitive doses of GC. Recently, Garnacho *et al.* [15], in a multicentre prospective study including patients with an ICU stay longer than 7 days, evidenced that both treatment with steroids (OR 3.5) and COPD (OR 2.9) were significantly associated with *Aspergillus* spp. isolation in respiratory secretions. In the present series, all but one patient on chronic long term GC treatment suffered fungal pneumonia and all of them had chronic pulmonary diseases. However, IPA affected not only patients with COPD but also with other chronic lung diseases such as chronic asthma, idiopathic pulmonary fibrosis and residual fibrotic post-TB lung lesions. This finding suggests that it is not the disease itself but rather the chronic alterations of the lung architecture that pose individuals at risk for fungal pneumonia if they require long term or repetitive doses of GC.

Clinical and radiological characteristics of IPA are often non specific and a high level of clinical suspicion is required for the diagnosis. Also, some of the diagnostic tools that are valuable in bone marrow transplant need to be evaluated in other groups of patients such as those treated with high dose GC. In the present series, galactomannan antigen was determined in three patients with probable IPA, and in all instances the result was negative, suggesting that sensitivity of this test might decrease in certain non-severe immunocompromised patients. Further studies evaluating the usefulness of this antigen determination with the specific cut-off points and serial determinations in non-immunocompromised patients are required. Similarly, in our population CT scanning of the lungs demonstrated low sensitivity for identification of specific signs of IPA. This confirms that in patients with normal neutrophil counts, a halo sign on CT scan is rarely seen and its absence in this population has no negative predictive power [16].

An early detection of invasive fungal infection is mandatory due to the uniformly poor prognosis with late treatment [9,10]. Unfortunately, the diagnosis of opportunistic lung infections is frequently delayed in patients taking high doses of GC, since an aggressive work-up for such infections is not always undertaken. In the present series, although performed relatively late, bronchoscopic techniques allowed the isolation of *Aspergillus* spp. in six cases. The concomitant isolation of other pathogens such as multi-resistant BGN or MRSA that occasionally co-infect patients with IPA is another potential benefit of performing a FOB exploration in these patients.

Although definitive diagnosis of IPA requires demonstration of tissue invasion on a biopsy specimen, several authors, in trying to achieve a provisional diagnosis, have required multiple cultures from respiratory specimens as an alternative [9]. Interestingly, when the number of positive samples was examined in a hospital-based survey of aspergillosis, 61% of those with confirmed IPA had a single positive culture result and only 18% had three positive culture results [17]. This suggests that requiring multiple positive results as a criterion for a diagnosis may underestimate the prevalence of this fungal infection [18].

Given the high mortality of IPA, and the potential benefits of an early treatment, institution of anti fungal prophylaxis in severe chronic respiratory patients requiring high or repetitive doses of GC should be investigated in adequate controlled trials. The prognostic implications of excessive delay in establishing a specific diagnosis and the high diagnostic yield of bronchoscopy favours the early employment of this technique once pulmonary infiltrates have been identified.

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