Treatment of severe forms of paracoccidioidomycosis: is there a role for corticosteroids?

GIL BENARD*, ALÉIA F. CAMPOS†, LUCAS C. NETTO†, LUIZ G. GONÇALVES†, LUIZ R. MACHADO‡, EVANTHIA V. MIMICOS†, FRANCISCO O. S. FRANÇA† & RONALDO C. B. GRYSCHEK†

*Laboratory of Medical Investigation Units 53 and 56, Dermatology Division of the Hospital das Clínicas, University of São Paulo Medical School and Laboratory of Medical Mycology, Tropical Medicine Institute, University of São Paulo, †Infectious Diseases Division, Hospital das Clínicas, University of São Paulo Medical School, and ‡Neurology Department, University of São Paulo Medical School and Systemic Mycoses Outpatient Unit, Infectious Diseases Division, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil

Despite their immunosuppressive effects, corticosteroids have long been used as adjunct therapy (aCST) in the treatment of infectious diseases. The rationale is that in certain infections it is necessary to decrease the exacerbated host’s inflammatory response, which can otherwise result in tissue damage and organ dysfunction. In fact, a major concern in treating paracoccidioidomycosis (PCM) is the host’s intense inflammatory response to *Paracoccidioides brasiliensis*, which can be further intensified by antifungal therapy. Depending on its localization, this immunological phenomenon may be life threatening or result in permanent sequelae, as is the case for some patients with cerebral or laryngeal involvement. However, the literature on aCST in paracoccidioidomycosis treatment is scarce and as a result we present our recent experience in the management of four patients with severe PCM manifestations, i.e., cerebral paracoccidioidal granuloma, laryngeal stenosis, compressive abdominal mass, and exacerbated inflammatory response with tissue destruction. In addition to the antifungal therapy, these patients required aCST, which probably promoted their clinical improvement and/or prevented serious complications. We suggest that aCST: (a) can potentially help in the management of selected cases of severe forms of PCM, particularly when there is a risk of acute complications, and (b) that it can be used safely provided that the risk-benefit ratio is carefully weighed. Well-controlled, prospective studies of aCST in the treatment of severe cases of paracoccidioidomycosis are needed to better define its role in the management of PCM.

Keywords paracoccidioidomycosis, corticosteroids, adjunct therapy, treatment, paradoxical response

Introduction

Despite their major immunosuppressive effects, corticosteroids have long been employed as adjunct therapy (aCST) in the treatment of infectious diseases [1]. The rationale for their use is that in certain situations it is crucial to decrease the host’s inflammatory response which, if left unchecked, could be harmful. This is exemplified by leprosy patients who develop reactional states which must be rapidly treated with immunosuppressive doses of prednisone in order to prevent permanent disabilities caused by the exacerbated inflammatory process that involves peripheral nerves [2]. aCST is also recommended for bacterial meningitis, severe pyogenic arthritis and in certain types of tuberculosis such as involving the pericardium and meninges [1,3]. There is
also some evidence of benefits of prednisone in lymph node and pulmonary tuberculosis [4,5]. The range of the applications of aCST has increased with the advent of AIDS as it is recommended in the management of certain opportunistic infections such as severe Pneumocystis jirovecii pneumonia [6].

On the other hand, aCST is rarely recommended for patients with systemic mycoses. Guidelines for the treatment of such infections which were recently reviewed recommended aCST for histoplasmosis involving severe pericarditis, arthritis, mediastinitis and acute pulmonary infection associated with hypoxemia [7]. In cryptococcosis, it may be considered in instances of cerebral infection associated with a mass effect and, in AIDS patients, with elevated intracranial pressure in the context of an immune reconstitution inflammatory syndrome (IRIS) [8]. On the other hand, aCST has not been recommended for coccidioidomycosis and blastomycosis [9,10], as well as paracoccidioidomycosis, the most important endemic mycosis affecting immunocompetent hosts in Latin America, including patients with neuroparacoccidioidomycosis (neuroPCM) [11–14]. Despite this, aCST has occasionally been used in the management of selected PCM cases at our University hospital with good results and no significant side-effects. In most cases, aCST was indicated due to the presence of neuroPCM, although the literature on this matter is scarce and somewhat contradictory. Neurosurgery has been considered the best alternative to treat complications of neuroPCM such as elevated intracranial pressure or the presence of mass effect caused by paracoccidioidal granulomas [11]. Sporadic case-reports referred to the use of corticosteroids [15–17], while other authors do not recommended it, preferring surgical drainage or stereotactic-guided removal of the granulomatous lesion [18]. Recently we described the use of aCST in two children with severe acute PCM and a paradoxical reaction to treatment, who had favorable outcomes [19].

Due to the lack of information regarding the use of aCST in paracoccidiomycosis, we present our recent experience in the management of four non-immunocompromised, HIV-uninfected patients with different clinical manifestations of PCM who required, and benefited from, aCST. Although based on a restricted number of cases, we propose that aCST should be considered in the treatment of selected cases of severe PCM.

Patients

Written informed consent was obtained from all four patients. The first case involved a 61-year-old man with a previous diagnosis of PCM causing an oral ulcerated lesion. Diagnosis was obtained through biopsy of this lesion, which showed a granulomatous reaction around typical *P. brasiliensis* yeast forms. Since there was no evidence of other organ involvements (the chest X-rays being normal), the patient was considered to have the chronic unifocal form of PCM and was prescribed sulfamethoxazole-trimethoprim (SMX-TMP). He also had type II diabetes mellitus that has been treated with oral medication. While the oral lesion healed, the patient was temporarily lost to follow-up studies. Three years later he was admitted to the emergency service with a history of progressive gait instability over the previous six months, including falls, vertigo and episodes of unprovoked vomiting and hiccups. Symptoms progressed to the point the patient had been unable to walk or sit upright for the month prior to admission. He noted that he had stopped the SMX-TMP treatment shortly after the oral lesion had healed. On admission, neurological exam disclosed an alert and cooperative patient, with severe trunk ataxia, with a tendency to fall to the left. There was bilateral gait ataxia, worse in the legs, more pronounced on the left side, preserved muscle strength and bilateral Babinski signs, tongue deviation to the right and horizontal and rotatory nystagmus, best elicited on right gaze. Brain magnetic resonance imaging (MRI) showed a heterogeneous contrast-enhancing lesion in left cerebello-pontine angle, involving the middle cerebellar peduncle and the medulla on the left, with mass effect and protruding onto the fourth ventricle (Fig. 1).

Although there was no oral or respiratory tract lesion suggestive of relapsed PCM, the patient was considered to

![Fig. 1](https://academic.oup.com/mmy/article-abstract/50/6/641/977201)
have a cerebelar and apendicular syndrome due to a paracoccidioidal lesion on the cerebellum. Anti-*P. brasiliensis* antibody titers detected by counterimmunoelectrophoresis (CIE) were positive (1:32) at that time of examination [20]. He was treated with intravenous SMX-TMP and dexametasone; the latter used at 16 mg/day for 6 days and then rapidly tapered off until complete cessation 7 days later when he was discharged to continue on oral SMX-TMP only. At discharge his ataxia symptoms had partially subsided, i.e., he could remain seated, walk short distances, and the nausea and vomiting disappeared. However, during this period it was difficult to control his diabetes and he occasionally required supplementary regular insulin. He is being followed at the outpatient service and after 6 months of SMX-TMP treatment his neurological symptoms had disappeared without sequels.

Patient 2, a previously healthy 38-year-old man, had an 8-month history of laryngeal pain, dysphagia, hoarseness and weight loss (∼15 kg) and sporadic cough. In addition, physical examination revealed small ulcerated cutaneous lesions (∼0.5 cm in diameter) over the face, left arm and back and cervical lymphadenopathy. Chest X-ray showed bilateral reticular interstitial infiltrates compatible with pulmonary PCM. A computed tomography (CT) scan of the neck showed cervical lymphadenopathy and an infiltrative laryngeal process with reduction of air passage (Fig. 2). The patient underwent a laryngoscopy, but before proceeding with biopsies of the laryngeal lesions, it was necessary to perform a tracheostomy due to the severe stenosis. The biopsies of the larynx and of a cutaneous lesion showed yeast forms with the morphology of *P. brasiliensis* (Fig. 3) and accordingly he was diagnosed as having the chronic multifocal form of PCM. Since the patient had to be fed through a nasoenteral cannula, it was determined to treat him with sulfadiazine in association with prednisone (1 mg/kg/day), in order to prevent total occlusion of the airway passage and to accelerate the subsequent removal of the tracheal cannula. After 10 days of treatment, a second laryngoscopy was performed, which showed significant reduction of the stenosis. Both the tracheal cannula size and the corticosteroid dose were then progressively reduced. At day 30 of hospitalization, the corticotherapy was halted, the tracheostomy was occluded and the patient started breathing normally and could ingest solid foods. A neck CT scan performed after 7 weeks of treatment showed normal air passage (Fig. 2). The patient’s conditions evolved without further complications and he continues to improve on sulfadiazine therapy only.

Patient 3, a previously healthy 44-year-old man, was referred to our service after being investigated elsewhere for a 2-month history of abdominal pain, weight loss, clinical deterioration and fever. Physical examination was unremarkable except for a diffuse tenderness at the abdominal upper left quadrant. An esophagogastroduodenoscopy was normal but the abdominal ultrasonography showed lymph node enlargements. An MRI revealed a conglomerate of coalescent inflamed lymph nodes around the mesenteric area. A biopsy was obtained through a videolaparoscopy procedure and based on this observation, a provisional report described the presence of yeast cells suggestive

![Fig. 2](https://academic.oup.com/mmy/article-abstract/50/6/641/977201) Cervical TC scan of patient 2 showing (a) laryngeal stenosis and (b) its resolution (arrows). Sections obtained at the arytenoid level 7 weeks apart.
of Cryptococcus spp. Treatment with fluconazole (800 mg/kg/day) was started but discontinued after three days when typical multiple budding yeast cells suggestive of *P. brasiliensis* were observed in Grocott stained sections (Fig. 3). The diagnosis of PCM was corroborated by the high titers (1:256) of anti-*P. brasiliensis* antibody on CIE. The patient was then treated with sulfadiazine (6 g/day) which resulted in the improvement of his general condition. However, 11 days after the beginning of the antifungal treatment, the patient was readmitted at the emergency service for an acute abdomen due to an intestinal sub-occlusion. The abdominal X-rays showed distended bowel loops with fluid levels. A CT showed a conglomerate of hypertrophied cervical and supraclavicular lymph nodes forming a cervical mass, some of them with suppuration, and a nasal lesion with necrosis and cartilage destruction (Fig. 4). A chest X-ray revealed bilateral diffuse reticulonodular infiltrates, typical of the pulmonary PCM. Fiberoptic laryngoscopy revealed ulcerated and infiltrative lesions in the nasopharynx and larynx extending to the vocal folds (Fig. 5). Direct examination of cutaneous lesions revealed typical *P. brasiliensis* yeast cells and biopsies of these lesions confirmed the diagnosis. Cervical CT scan showed the presence of multiple lymph nodes with necrosis and liquefaction in the retropharyngeal, laryngeal and peri-hilar lymph nodes. Patient was diagnosed as having the chronic multifocal form of PCM with a prominent inflammatory response that resulted in necrosis and tissue destruction, especially of the oro-nasal and tracheal airway. Considering the exacerbated inflammatory process, it was decided to introduce prednisone (1 mg/kg) to the antifungal regimen (sulfadiazine 100 mg/kg/day). He responded well to this strategy, with significant, although still incomplete, reduction of the cutaneous inflammatory lesions and improvement of the dysphagia and hoarseness within a few days. He was kept on a full dose of prednisone for 10 days, after which it was tapered off until complete removal after 30 days. He is currently on sulfadiazine therapy, with marked clinical improvement and healing of the cutaneous lesions.

**Discussion**

A major concern in the treatment of severe forms of PCM is the intense inflammatory response induced by *P. brasiliensis*, which, in the short term, may cause severe tissue damage and impairment of organ function, and, as a long-term consequence, fibrosis and retraction [21–24]. This inflammatory response can be intensified by the antifungal...
therapy, as in cases of tuberculosis or leprosy [25], due to the release of antigenic components from the dead cells of the etiologic agent caused by treatment. In fact, in some patients, the anti-\textit{P. brasiliensis} antibody titers rise in the first weeks of treatment, probably in response to the increased antigen exposure [GMB Del Negro and MSM Vidal, personal communication]. Moreover, depending on the localization, this exacerbated inflammatory response might be life threatening, as in patients with CNS or laryngeal involvement [unpublished data, 26]. In fact, although PCM is usually recognized as a disease associated with high morbidity but low mortality, the outcome of patients with the cerebral form of the disease is poor, with mortality rates ranging from 35–46%. However, it should be noted that some studies involving small numbers of cohorts reported lower rates [12,27–30]. Moreover, among survivors, up to 50% presented with some neurological impairment [12]. In a review of cases from a single center, no deaths were reported but severe residual neurological deficits were observed in 57% of the patients [31]. In our service, aCST has occasionally been used to treat those with cerebral PCM whose lesions present a mass effect or significant perilesional edema. Worsening of these lesions could represent a risk of herniation to these patients, as illustrated in our first case. The risk of complications due to the localization (medulla) of the paracoccidioidal granulomatous lesion,
presenting with perilesional edema, was decisive in our introducing the use of prednisone with the antifungal drug. The prednisone was started at 16 mg/day, and then rapidly tapered once the neurological symptoms begin to subside.

Patients with laryngeal PCM may develop tracheal stenosis and require tracheotomy due to the risk of asphyxia as the edema and stenosis worsen with antifungal therapy. Death by asphyxia in these patients has been reported [32] and aCST has been recommended as an adjunct therapy by some authors [33]. Patient 2 is an example of this situation and the rapid improvement and early removal of the cannula suggest the benefit of the association of aCST with the antifungal.

Patient 3 illustrates the deleterious effect of exacerbation of the inflammatory process which may be caused by the use of antifungal drugs. The patient had the acute, most severe form of PCM, which is mainly characterized by lymph nodes involvement. The inflammatory process frequently progresses to the destruction of the node architecture and formation of fistulas. When adjacent lymph nodes are involved, they may fuse and form tumoral masses as frequently seen in patients with abdominal lymphadenopathy [17]. In this patient, the tumor compressed the transverse colon resulting in intestinal sub-occlusion. Usually, this complication is managed through an exploratory laparotomy but this would not only represent an additional risk but this complication is managed through an exploratory laparotomy. When adjacent lymph nodes are involved, they may fuse and form tumoral masses as frequently seen in patients with abdominal lymphadenopathy [17]. In this patient, the tumor compressed the transverse colon resulting in intestinal sub-occlusion. Usually, this complication is managed through an exploratory laparotomy but this would not only represent an additional risk to the patient but also significantly increase the potential morbidity of our patient who had a severe illness. aCST was found to be a positive addition to the therapeutic regimen.

Patient 4 also presented with suppurated and hypertrophied cervical lymph nodes. In addition, a nasal lesion progressed to a large ulcer with destruction of the nasal cartilage and the extensive and destructive laryngeal involvement was also a concern in this patient. For these reasons it was decided to treat the patient with aCST (prednisone 1 mg/kg) and sulfadiazine to achieve a faster recovery.

These case reports suggest that selected PCM patients can benefit from the use of aCST. Indications for the inclusion of aCST for treating infectious disease have been recently reviewed [34]. Since the number of well-controlled studies is limited, it has been used in many situations, but in only a small number of cases has aCST clearly proven beneficial. Together with our previous report of two children with the acute form of PCM and paradoxical reaction to treatment, for whom aCST seemed to prove to be part of their successful outcome, these four additional cases reinforce our view that aCST can be of benefit for some PCM patients. Provided that it is used for short periods (<1 month of total duration of treatment, including the time required to taper off the drug), side-effects may be minimal as in our patients. Thus, aCST might be eventually considered in severe cases of cerebral paracoccidioidal granulomas, severe laryngeal stenosis, compressive abdominal masses and exacerbated inflammatory responses resulting in tissue destruction.

The experience with aCST in the treatment of infectious diseases shows that it does not interfere with the effectiveness of the antimicrobial therapy [34]. This has been largely demonstrated with other chronic granulomatous diseases, such as TB and leprosy, both of which share some similarities in their immunopathogeneses with PCM. There were no reports showing that the immunosuppressive therapy resulted in increased microbial burdens, even in AIDS patients [35]. In fact, our experience also suggests that the microbiological response to the antifungals remained unaffected. Nevertheless, because of the potential side-effects, the risk-benefit ratio of aCST should always be weighed carefully. However, review of the literature indicates that aCST is quite safe [34] and in our patients, special care was taken to optimize its use for as short a duration as possible with treatment of no more than one month. A possible adverse effect was found only with the patient in case 1, who required regular insulin doses to control his type 2 DM. In order to minimize these side-effects, glucocorticosteroids with reduced mineralocorticoid activity are generally used. Prednisone at doses of 1 mg/kg/day was used in the treatment of our patients, based on the significant experience gained with its use in cases of leprosy [2]. However, when an intravenous route is required, as it generally happens in cerebral PCM, dexamethasone has been the drug of choice, due to its comparatively prolonged biological half-life and lack of mineralocorticoid action (36–54 h). Hydrocortisone is also a good alternative for use in these same patients as it has a rapid and short duration of action, the latter facilitating its swift discontinuation. Nevertheless, studies comparing the efficacy and side-effects of the different drugs in these situations are lacking. In addition, it is necessary to rule out subclinical associated infections such as tuberculosis and strongyloidiasis which may become severe and disseminated with corticotherapy.

The main objectives of this report were to provide evidence that aCST (a) can potentially help in the management of selected cases of severe forms of PCM, particularly when there is a risk of acute complications, and (b) can be safely used, provided the risk-benefit ratio is carefully weighed. These considerations may eventually be useful in the care of patients with other endemic systemic mycoses. In fact, indications for aCST are expanding taking into account that the deleterious effects of the host’s inflammatory response are being increasingly recognized [36]. Although it is suggested that in all four cases presented here that CST fostered clinical improvement and/or prevented serious complications, no definitive conclusions can be
made with regard to its efficacy due to the restricted number of patients. Finally, resolution of PCM is often followed by intense fibrotic scars and sequels, which is another major concern in PCM treatment [22]. Although it was not the purpose of this report, reduction of the fibrosis and sequels of the treated patients could eventually be another benefit of aCSIT. Other anti-inflammatory drugs such as pentoxycyline have been tested in experimental PCM models and have shown promise [37]. These and other aspects of adjunct anti-inflammatory therapy of PCM and other endemic mycoses warrant well-controlled studies.

Acknowledgements

We would like to thank Dr Thelma Okay for expert advice in preparing the manuscript.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

33 do Valle AC, Apreliano Filho F, Moreira JS, Wanke B. Clinical and endoscopic findings in the mucosa of the upper respiratory


This paper was first published online on Early Online on 6 February 2012.
