2012

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MEDICAL MYCOLOGY, LONDON, v. 50, n. 4, pp. 407-411, MAY, 2012

Medical Mycology May 2012, **50,** 407–411

informa
healthcare

Fatal septic shock due to a disseminated chronic form of paracoccidioidomycosis in an aged woman

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Once rare, septic shock (SS) due to disseminated fungal infections has been increasingly reported due to a growing number of immunocompromised patients, but remains rare in non-immune-compromised individuals. In paracoccidioidomycosis, it has been described in only three patients with the severe, acute form of the disease. We describe the development of a refractory, fatal septic shock due to a severe disseminated chronic form of paracoccidioidomycosis in an older woman without any other microbial insults. A striking event in the evolution of her case was the severe depletion of lymphocytes from the peripheral blood and lymphoid organs. Lymphocyte depletion due to apoptosis is described in the late phase of sepsis and can contribute both to immunosuppression and the progression of SS. The possible mechanisms involved in the induction of SS in the chronic form of paracoccidioidomycosis are discussed.

Keywords paracoccidioidomycosis, septic shock, apoptosis, lymphopenia

Introduction

Once rarely reported, septic shock (SS) due to disseminated fungal infections has been increasingly described due to a growing number of immunocompromised patients. Transplant recipients and patients undergoing chemotherapy are those at highest risk [1,2]. In most cases, these infections are caused by otherwise opportunistic fungi of which *Candida albicans* is the most frequent pathogen. In fact, *Candida* spp. have become the fourth most common etiologic agent of sepsis in several ICUs and *Candida*-induced septic shock has been described in up to 15% of the patients with sepsis [3]. On the other hand, severe disseminated forms of the endemic mycoses can also progress to SS in immunocompromised patients. This has been described primarily in disseminated histoplasmosis or coccidioidomycosis in the context of HIV infection [4,5]. In contrast, SS has been very rarely described in systemic mycoses of non-immune-compromised hosts. There have been a few reports of SS in coccidioidomycosis and blastomycosis patients which were either associated with, or preceded by, acute respiratory distress syndrome (ARDS) [6,7]. It was reported that 2% of the patients admitted with coccidioidomycosis at a reference hospital during the 1991–93 epidemics developed septic shock [8]. In paracoccidioidomycosis (PCM) there are three published reports of patients with the acute, more severe form of the disease, who developed septic shock and, in two of them in association with ARDS. We present here a patient with the chronic form of the PCM who developed refractory, fatal septic shock and discuss the possible mechanisms underlying this occurrence.

Received 12 August 2011; Received in final form 3 September 2011; Accepted 6 October 2011

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Case report

A 72-year-old woman from Parana State, a paracoccidioidomycosis endemic area in Southern Brazil, was seen at

DOI: 10.3109/13693786.2011.630685

our outpatient service on January 2010. She reported weight loss over the last year, as well as changes of her intestinal habits, i.e., alternating periods of diarrhea and constipation. One month before admission, she acquired symptoms of progressive dysphagia and daily fever. Previous significant medical conditions were mild and controlled hypertension, smoking habit, and a gastric ulcer diagnosed eight years earlier. Physical examination revealed a patient in normal condition, febrile (38.8°C), with a respiratory rate of 16 breaths/min and heart rate of 68 beats/min. Heart, lungs, neurological and abdominal examinations were unremarkable except for a discrete hepatomegaly of 3 cm below the costal margin. There was also a cervical micropolyadenopathy. Laboratory tests and imaging exams were requested and a new visit scheduled for 30 days later. However, the patient's general condition further deteriorated and she was admitted three weeks afterward at the emergency service.

At admission, she was dehydrated, presenting altered mental status, tachycardia, hypotension (80×50 mmHg), basal crackles in lung bases, diffuse abdominal pain without peritonitis signals, discrete hepatosplenomegaly and cervical micropolyadenopathy. Laboratory tests from her first visit showed mild anemia (10.8 g/dl), a discrete leukocytosis (13300/mm^3), eosinophilia (2500/mm^3, a feature compatible with disseminated forms of PCM), 1436/mm^3 lymphocytes (normal range 1000–4000/mm^3), and normal platelets count. Acute phase reactants were all elevated and there was a marked hypergamaglubulinemia (2.4 g/dl). A chest X-ray showed a bilateral micronodular infiltrate sparing the lower lobes, compatible with active pulmonary PCM. A thoracic computed tomographic scan was also suggestive of PCM, showing disseminated micronodules and bronchial wall thickening (Fig. 1). An abdominal CT scan showed hepatosplenomegaly and enlarged para-aortic, mesenteric and hepatogastric lymph nodes (up to 2 cm in diameter) but the adrenals were normal. Blood tests collected at the emergency room showed anemia (10.3 g/dl), thrombocytopenia (121000/mm^3), 10100 leukocytes/mm^3 with severe lymphopenia (101 cells/mm^3), the C-reactive protein was elevated (190.7 mg/l) and the lactate was markedly increased (164 mg/dl (normal range $>$14.4 mg/dl). Liver tests and coagulation times were all mildly to moderately abnormal.

Despite initial volemic resuscitation and use of vasoactive amine, she presented neurological deterioration and was transferred to the ICU. The patient required endotracheal intubation and mechanical ventilation. Noradrenaline at doses up to 2.5 μg/kg/min was administered, without adequate hemodynamic effect and methylene blue was associated. The patient died of refractory septic shock 24 h after ICU admission. Blood and urine cultures were sterile for bacteria; no cultures for fungi were available.

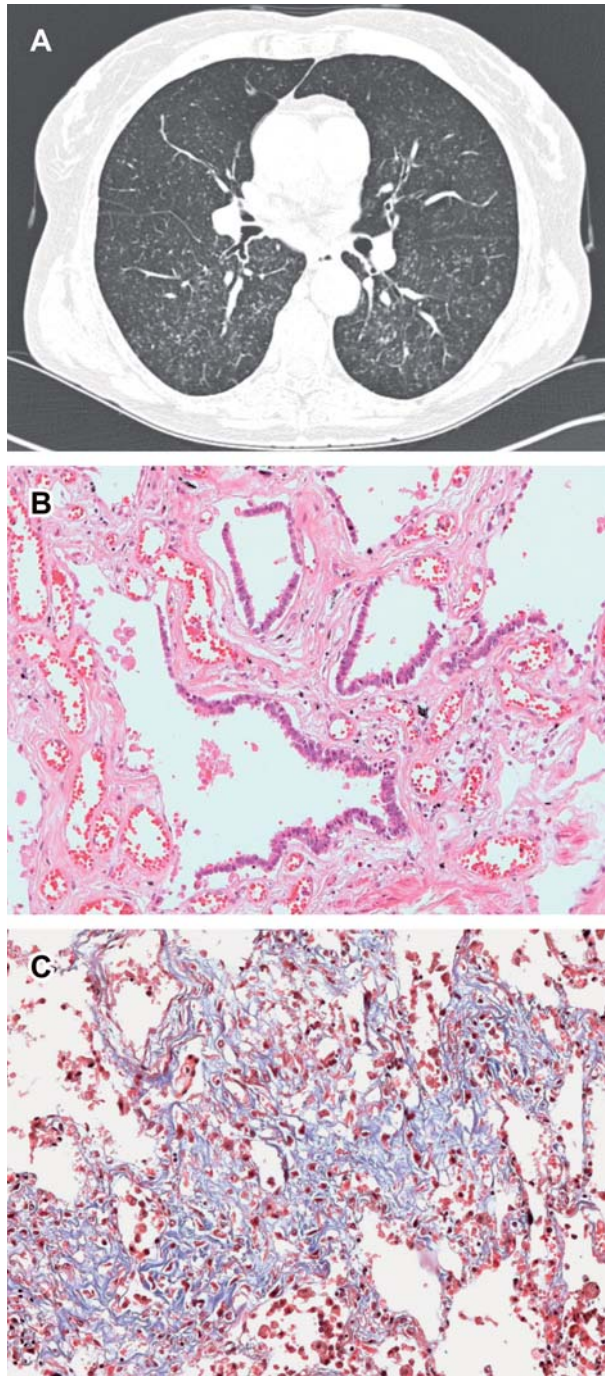

Fig. 1 (A) Computed tomography of the chest showing disseminated micro-nodules and bronchial wall thickening, both characteristic of chronic pulmonary paracoccidioidomycosis. Lung histological sections stained with (B) hematoxilin eosin and (C) Masson showing extensive interstitial fibrosis, suggestive of the chronic nature of the pulmonary involvement. Magnification: 200×.

Diagnosis of disseminated PCM was made only at autopsy, at which time she was found to have compromised lungs (Fig. 1 and 2), spleen, liver (Fig. 3), and enlarged (up

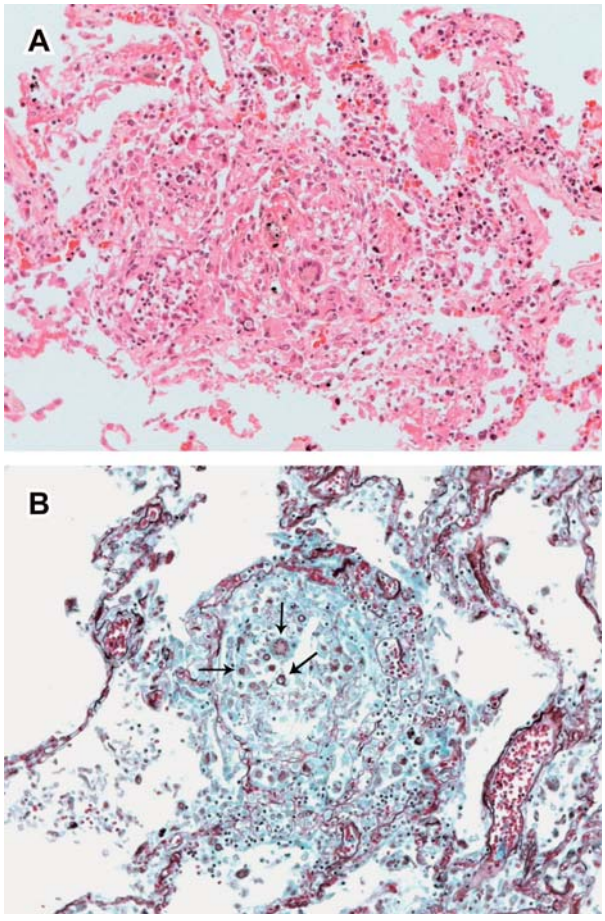

Fig. 2 Lung histological sections stained with (A) hematoxilin eosin and (B) Grocott showing a granulomatous reaction and typical *Paracoccidioides brasiliensis* multiple budding yeast cells (arrows), indicative of an active fungal infection. Magnification: 200×.

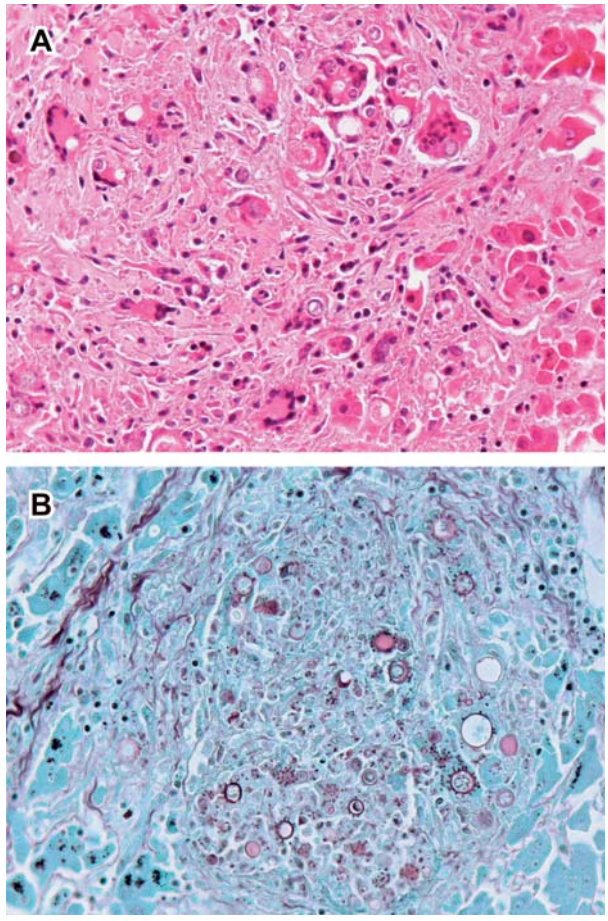

Fig. 3 Liver histological sections stained with (A) hematoxilin eosin and (B) Grocott showing a granulomatous reaction and many typical *Paracoccidioides brasiliensis* multiple budding yeast cells, indicative of the dissemination of the fungal infection. Magnification: 400×.

to 3.5 cm) mediastinal, para-aortic, peri-splenic, perirenal, pericolonic, mesenteric as well as cervical and other superficial chains of lymph nodes. In all lymphoid organs examined there was marked lymphocyte depletion, replaced by an inflammatory infiltrate and areas of necrosis. There were also signs of septic shock such as congestion of the liver, spleen, kidneys, and gastric mucosa.

Discussion

This case report presents a very unusual feature, the development of fatal septic shock in an older woman with the chronic form (CF) of paracoccidioidomycosis. The patient did not have any evidence of other microbial infections. The only three published fatal cases of PCM due to septic shock occurred in young patients with the acute form (AF) of the disease [9–11]. In two of them, the SS was preceded by ARDS [10,11]. The AF of PCM is characterized by rapid progression and dissemination of the disease from the primary pulmonary infection [12]. In contrast, the hallmark of the CF is the slow progression of the disease after reactivation of the etiologic agent from quiescent foci [12]. Thus in the CF form, although frequently multifocal [13], the delayed emergence of the clinical manifestations and its protracted evolution seem to reflect some partial control of the infection by the patients' immune response. This is in contrast with the AF where the anti-*Paracoccidioides brasiliensis* cell mediated immunity is severely compromised [14].

SS is defined as the final result of complex interactions between the pathogen and the host immune response, and factors related to both the microorganism and the host play a role in the development of this clinical condition [15]. It ultimately reflects an inappropriate response of the host to a microbial pathogenic insult [15]. However, SS is a rare event in systemic mycoses, and has most often been described in immunocompromised patients [4,5]. Fungi lack endotoxins or other components that are capable of

triggering exacerbated immune responses such as the lipopolysaccharide of Gram-negative bacteria or peptidoglicans of Gram-positive bacteria. The mechanisms by which SS is triggered in disseminated fungal infections are not known. In *Candida* spp., several cell wall surface components such as mannanns, β-glucans, phospholipomannan and 0-linked mannosyl residues are recognized by toll like receptors and other pathogen-associated receptors (PRR) [16]. In certain patients, this may lead to exacerbated immune responses and SS. However, the reasons why SS occurs more frequently with some fungi than others, and more frequently in severely immunocompromised than those not so significantly immunocompromised, remain unclear.

P. brasiliensis elicits strong inflammatory responses, but the acute inflammatory phenomena associated with exacerbated immune responses that predispose to SS are rarely seen. Some studies investigated the components of the innate immune response that mediate the inflammatory response in PCM infection, mainly in experimental infection models [17–20]. However, there is a wide variability in their conclusions depending on the model (intra-tracheal vs. blood borne), inoculum, mouse strain used, among other factors. Moreover, the natures of the fungal components that trigger these responses remain unknown since whole viable yeast cells were used in these experiments. Evidence for and against a role of several PRR, such as Toll like receptors 2 and 4, adaptor intracellular molecule MyD88, mannose receptor and complement receptors, in the recognition of *P. brasiliensis* yeast cells has been provided [17–20]. A study suggests that TLR2, TLR4 and dectin-1 participate in the *in vitro* recognition and internalization of the fungus by human monocytes and neutrophils [21]. Thus a clear picture elucidating how *P. brasiliensis* could trigger an uncontrolled immune response leading to SS is still lacking.

However, the concept that SS is due to a hyper-inflammatory state has become a simplistic view [16]. It is now evident that many patients experience a systemic hypo-inflammatory state, often in the later phases of the septic shock. It has been shown that repeated insults by microbial products result in less profound physiologic alterations than those observed at earlier phases of severe sepsis [22,23]. Irrespective of the nature of the signaling pathways and fungal molecules involved in the triggering of the SS, a striking event in the development of PCM in our patient was the severe depletion of lymphocytes from the peripheral blood and lymphoid organs (Fig. 4). Apoptosis of lymphocytes, especially of CD4 + T cells, has been recognized as an important feature of sepsis and a key event in the immunosuppression seen in advanced phases of sepsis [24]. It is also a likely explanation for at least part of the lymphocyte depletion of our patient. Studies on the frequency of apoptotic lymphocytes could not be done because the autopsy was performed several hours after the patient's death.

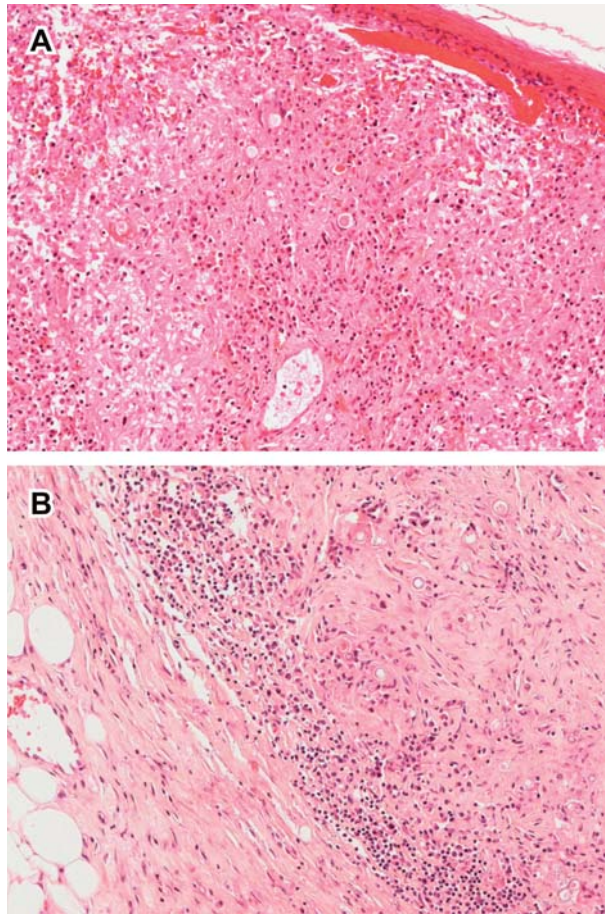

Fig. 4 (A) Spleen histological section showing depletion of the lymphocyte population. (B) Lymph node histological section showing replacement of the normal lymphoid follicular population by a granulomatous inflammatory process. Magnification: 200×.

Our hypothesis is that the patient presented a chronic, slowly evolving pulmonary form of PCM, as suggested by the simultaneous presence of granulomas with fungi and fibrosis in the lungs (Fig. 1 and 2). However, due to the conjunction of delayed diagnosis and failure of the host's immune system in restraining the fungi within the granulomatous reaction, the infection progressed to a disseminated disease (Fig. 3) and, subsequently, to sepsis. This was later associated with lymphocyte depletion (Fig. 4), probably due to apoptosis and invasion of the lymphoid organs by the inflammatory infiltrate and, as a consequence, in cell mediated immunosuppression. The lack of cell mediated immune mechanisms resulted in further increase in the fungal load (a frequent event in PCM of immune-compromised patients [25]) and uncontrolled activation of the innate immune response, both of which lead to the

development of SS. Devising experimental models mimicking this clinical condition is needed to determine the fungal and host factors involved in this process and the ways to curtail it.

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

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This paper was first published online on Early Online on 21 November 2011.