Usefulness of corticosteroid therapy during chronic disseminated candidiasis: case reports and literature review

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Objectives: Chronic disseminated candidiasis (CDC) is a disseminated fungal infection that is frequently seen in patients undergoing intensive treatment of haematological malignancies. The first signs of CDC appear during neutrophil recovery. Clinical and physiopathological characteristics of CDC suggest it belongs to the spectrum of fungus-related immune reconstitution inflammatory syndrome (IRIS). We report five cases of CDC treated with antifungal therapy and adjuvant corticosteroids to decrease the exacerbated inflammatory response.

Methods: We conducted a retrospective study in the Haematology Department of the University Hospital of Tours, France. The five reported cases were treated for CDC with antifungal therapy and adjuvant corticosteroids.

Results: Of the five cases of CDC, one was proven and four were possible, according to the 2008 European Organization for Research and Treatment of Cancer (EORTC) classification. All patients were being treated for acute leukaemia. In all cases, symptoms disappeared 2.8 days (range, 1–7) after the beginning of adjunctive corticosteroid therapy. Corticosteroids were administered on average for 146 days (range, 4 weeks–1 year) and antifungal therapy was administered for the duration of chemotherapy consolidation. There was no exacerbation of CDC symptoms during the next round of chemotherapy or bone marrow transplantation. One patient died from relapse of leukaemia.

Conclusions: Within the framework of IRIS, adjuvant corticosteroid therapy could rapidly improve CDC symptoms and allow continued chemotherapy without delay and without compromising the haematological prognosis.

Keywords: systemic inflammatory response syndrome, corticoids, neutropenia, leukaemia

Introduction

Chronic disseminated candidiasis (CDC) is a severe form of disseminated fungal infection that affects mainly the liver, the spleen and, occasionally, the kidneys. The incidence of this form of candidiasis has increased with increasingly aggressive use of chemotherapy and is responsible for prolonged neutropenia. CDC is estimated to occur in <5% of patients treated for acute leukaemia.¹,²

CDC develops in two stages: first, yeast haematogenous dissemination occurs during aplasia; second, the neutrophil recovery phase is marked by a ‘paradoxical’ revelation, with recurring fever, hepatopathy and the appearance of hepatic and splenic micronodules.³ During the second phase, the lack of evidence supporting a fungal infection suggests CDC belongs to the spectrum of immune reconstitution inflammatory syndrome (IRIS).³

Regarding treatment of IRIS, we hypothesize that adjuvant corticosteroids could accelerate recovery.³ We report five cases treated with antifungal therapy and adjuvant corticosteroids, and review all published cases of CDC treated with adjuvant corticosteroids.

Methods

We performed a retrospective study in the Haematology Department of the University Hospital of Tours, France, between 2005 and 2009. The five reported cases were hospitalized and treated for CDC with antifungal and corticosteroid therapy. According to the revised definition of invasive fungal disease from the European Organization for Research and Treatment of Cancer (EORTC) in 2008, CDC is classified as ‘proven’, ‘probable’ or ‘possible’.³

Results

We describe five cases of CDC, one proven and four possible, according to the 2008 EORTC classification. All patients were being treated for acute leukaemia with repeated intensive
For the other patients, symptoms became apparent on average 4.4 days (range, 3–7) after neutrophil recovery with hepatic, fever and, in one case, icterus.

**Paraclinical investigations**

CDC was associated in all cases with an increase of inflammation markers (C reactive protein and fibrinogen) and cholestasis, and in three cases with hepatic cytolysis.

For four patients, radiological investigations (abdominal ultrasound and CT scan) revealed signs consistent with hepatosplenic fungal lesions 1 day after CDC was first suspected. In one case, the appearance of lesions was delayed for 60 days for CT and magnetic resonance imaging, and 80 days for ultrasound. In two cases, the CT monitoring showed an initial increase in micronodules with no correlation to a positive clinical outcome.

**Microbiology**

A biopsy of hepatic lesions was performed for three patients. In two cases, histopathological examination and culture revealed polymorphic nuclear cells associated with lymphocytes and granulomatous lesions, but no fungus. In one case, two histological investigations were performed: the first, following splenectomy for a capsular haematoma, revealed splenic abscesses containing yeasts; in the second, a liver biopsy for an increase in hepatic nodules, performed 11 months after neutrophil recovery, revealed fibrosis areas and polymorphic nuclear cells without fungal agent. No patient had a positive blood culture for fungus.

**Therapeutic and clinical evolution**

Frequently, multiple antifungals were prescribed for the same patient because of persistent fever. In all cases, antifungal therapy was maintained during consolidation chemotherapy.

The mean interval between fever recurrence and the beginning of corticosteroid therapy was 23.8 days (range, 3–59). Fever always disappeared, on average 2.8 days (range, 1–7) after starting corticosteroids. In one case, even though corticosteroids and fluconazole were maintained, there was a recurrence of fever without exacerbation during the second haematopoietic recovery. This led to a switch in antifungal treatment. Corticosteroids were administered for a mean duration of 146 days (range, 4 weeks–1 year). The dose was reduced progressively on the basis of clinical and biological parameters.

Chemotherapy was delayed in two cases. For the first patient, haematological treatment was briefly reduced because CDC was complicated by a spleen capsular haematoma; corticosteroids were introduced 46 days after surgery. For the second patient, treatment was delayed because fever persisted for a long time. Introduction of corticosteroids was postponed because CT revealed hepatosplenic nodules 60 days after symptoms. One patient underwent bone marrow transplantation 240 days after CDC. One patient died of relapse of leukaemia without evidence of active infection, and four were alive 3 years after the onset of CDC.

**Discussion**

We have described five cases of CDC treated with long-term antifungal therapy and adjuvant corticosteroids. Initiating
corticosteroid therapy both caused a rapid disappearance of symptoms and allowed continued chemotherapy without compromising the haematological outcome.

As far as we know, only four published studies have proposed adjuvant corticosteroids in CDC treatment. First, in 2007, Conter et al. prescribed 1 mg/kg/day of corticosteroids for one patient with CDC after 36 days of ineffective antifungal therapy; fever disappeared in 1 day without recurrence and corticosteroids were continued for 120 days. Second, in 2008, Legrand et al. reported 10 cases (first presented in a poster session, ICAAC 2005). Administration of 0.66 mg/kg/day (range, 0.4–2) of corticosteroid led to resolution of clinical signs in 4.5 days (range, 1–30). Corticosteroids were maintained for 109 days (range, 49–240) without recurrence of CDC. Third, in 2009, Saint Faust et al. treated two children with 1 mg/kg/day of corticosteroids for 45 days (range, 30–60), which improved clinical abnormalities in 1.5 days without relapse. Finally, in 2010, Chandresris et al. reported a case of exacerbation of CDC after administration of pegylated granulocyte colony stimulating factor; this was also treated successfully with 0.5 mg/kg/day of adjuvant corticosteroid for 51 days. In these studies, liver biopsy cultures were performed for all patients, and these were always negative except for one patient who did not receive antifungal treatment before undergoing biopsy. Histological examination revealed granulomatous lesions in 10 cases.

IRIS was first described in HIV-infected patients and is defined as the appearance of inflammatory disorders and clinical worsening of a treated opportunistic infection that cannot be explained by a reinfection. IRIS is also observed in haematological malignancies, autoimmune disease and transplantation when administration of immunosuppressive agents ended. With a better understanding of CDC physiopathology, the presence of clinical signs that correspond more to IRIS characteristics than to infectious disease leads to the hypothesis that CDC belongs to the spectrum of fungus-related IRIS, for example: symptoms occurred during neutrophil recovery while other disease infections improved; antifungal therapy was inefficient, suggesting therapeutic escape; cultures of liver biopsies were frequently negative but showed granulomatous lesions; intensive consolidation chemotherapy or haematopoietic stem-cell transplantation was (untypically) able to be continued without recurrence or fatal complication of the fungal infection; and, there were relatively few deaths due to CDC (reported at 0%–17% in different studies). The pathogenesis of CDC could be explained in two phases. First, during neutropenia, the presence of mucositis or ulcerations along the gastrointestinal tract damaged by chemotherapy would facilitate the translocation of yeasts colonizing the gastrointestinal tract into the bloodstream. Deficiencies in the host's immune defences would lead to the dissemination of Candida species and result in seeding in the liver and spleen. Second, during neutrophil recovery, clinical and radiological symptoms may appear due to the recovery of pathogen-specific immunity. Immunity against Candida species is characterized by proinflammatory Th1 and Th17 response and the production of cytokines such as tumour necrosis factor-α (TNF-α) and interferon-β (IFN-β). This appropriate response rapidly becomes excessive with an immunological Th1/Th17–Th2/Treg imbalance in favour of Th1/Th17, responsible for the formation of granulomatous lesions in tissue containing the pathogenic agent. Corticosteroids, by inhibiting secretion of pro-inflammatory cytokines and increasing the anti-inflammatory cytokine IL10, could modulate this paradoxical inflammatory response.

At present, adjuvant corticosteroid therapy is not recommended by the Infectious Diseases Society of America (IDSA). The IDSA recognized corticosteroids as a novel approach to treatment and declared that 'additional studies will be required in order to establish the benefit of this approach'. Nevertheless, for the 14 published cases as well as our 5 cases receiving adjuvant corticosteroids, CDC symptoms improved rapidly without secondary exacerbation or death due to fungal infection. Consequently, adjuvant corticosteroid therapy might well be an important approach for CDC treatment and should be prospectively evaluated in future studies.

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**Transparency declarations**
None to declare.

**References**