Mycopathologia (2023) 188:873–883
https://doi.org/10.1007/s11046-023-00755-9

ORIGINAL ARTICLE

Epidemiology, Clinical Characteristics and Risk Factors for Severity of Chronic Disseminated Candidiasis in Jerusalem, Israel

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Received: 14 April 2023 / Accepted: 25 May 2023 / Published online: 16 June 2023

Abstract Chronic disseminated candidiasis (CDC) occurs mostly in patients with acute hematologic malignancy and its clinical manifestations derive from immune reconstitution following neutrophil recovery. The aim of this study was to describe epidemiological and clinical characteristics of CDC and define risk factors for disease severity. Demographic and clinical data were collected from medical files of patients with CDC hospitalized in two tertiary medical centers in Jerusalem between 2005 and 2020. Associations between different variables and disease severity were evaluated, as well as characterization of *Candida* species. The study included 35 patients. CDC incidence slightly increased during study years and the average number of involved organs and disease duration was 3 ± 1.26 and 178 ± 123 days, respectively. *Candida* grew in blood in less than third of cases and the most common isolated pathogen was *Candida tropicalis* (50%). Histopathological or microbiological workup in patients who underwent an organ biopsy demonstrated *Candida* in about half of the patients. Nine months after starting antifungals, 43% of the patients still didn't have resolution of organ lesions in imaging modalities. Factors associated with protracted and extensive disease were prolonged fever prior to CDC and absence of candidemia. A C-Reactive Protein (CRP) cutoff level of 7.18 mg/dL was found to predict extensive disease. In conclusion, CDC incidence is increasing and the number of involved organs is higher than previously described. Clinical factors such as fever duration prior to CDC and absence of candidemia can predict severe course of disease and assist in treatment decisions and follow-up planning.

Handling Editor: Ferry Hagen

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11046-023-00755-9.

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Keywords Chronic disseminated candidiasis · Hepatosplenic candidiasis · Hematological malignancy · Risk factors · *Candida*

Introduction

Invasive candidiasis or candidemia is a common cause of nosocomial blood stream infection (BSI) with significant crude mortality rates of 10–47%, and attributable mortality rate of 28%, despite effective antifungal treatment [1–4]. Risk factors for candidemia include immunosuppression, hematologic malignancies, broad-spectrum antibiotics, intensive care unit (ICU) stay $\geq$ 72 h, central venous catheters (CVC), total parenteral nutrition (TPN) and invasive procedures [4, 5].

Chronic disseminated candidiasis (CDC) also known as hepatosplenic candidiasis (HSC) is a unique clinical manifestation of invasive candidiasis that occurs almost exclusively in patients with hematologic malignancies, particularly acute leukemia, although it has also been reported in patients with lymphoma, aplastic anemia and sarcoma [6]. The presumed mechanism of the disease involves the invasion of low inoculum *Candida* species from the gastro-intestinal (GI) tract into the hepatosplenic sinusoids through the portal circulation, following prolonged neutropenia and chemotherapy-induced mucosal damage [6]. In most cases of CDC, candidemia during the period of neutropenia is not evident and only 20% of blood cultures grow *Candida* species [7, 8]. Consequently, there is a significant involvement of the liver and spleen during CDC manifested on imaging studies as small target-like abscesses (bull's-eye lesions) [8], although other organs such as the lungs and kidneys can also be involved [6, 8]. The host response appears to be of great importance in the development of CDC since typical histology of affected organs shows granulomatous rather than pyogenic inflammation and clinical and imaging manifestations appear shortly after neutrophil recovery [8–10]. According to experimental studies in mice, CDC is an expression of immune dysregulation with a preference for Th1/Th17 pathways over Th2/Treg [8]. The incidence of CDC in high-risk patients is 3–29% but has decreased over the years due to the widespread use of antifungal prophylaxis [8]. Typical clinical manifestations include prolonged fever, right upper quadrant pain, and enlargement of the liver and spleen, with an increase in alkaline phosphatase [8].

According to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG), a definite diagnosis is based on a biopsy of an involved organ demonstrating granulomas and yeasts or pseudohyphae [11, 12].

Since biopsy is not always feasible in patients with hematologic malignancies, the diagnosis is frequently based on appropriate clinical, laboratory, and imaging findings [8].

Although the most common causative agent for invasive candidiasis is still *Candida albicans*, during the last decades and as a result of increased use of fluconazole, there is a change in species distribution causing invasive candidiasis, with an increase in the relatively azole-resistant *C. glabrata* comprising up to 38% of the cases [13–16]. Considering this change there is little contemporary data regarding epidemiology and outcomes of CDC.

In this study, we aimed to determine the clinical characteristics and outcomes of CDC in hospitalized children and adults in Jerusalem in recent years, as well as to define risk factors for the severity of the disease.

Materials and Methods

Study Design

A descriptive observational study, based on information collected from electronic medical files of patients hospitalized at Hadassah Medical Center and Shaare-Zedek Medical Center in Jerusalem, serving a population of a million. Included in the study were patients with a diagnosis of CDC from 2005 through 2020. The study was approved by the local IRBs (0331/19-HMO and 0225/19-SZMC).

Patients

Study cases were selected following a search of an electronic medical database for CDC, HSC, invasive candidiasis and candidemia diagnoses in patients admitted to the hematology, pediatric hemato-

oncology and bone marrow transplantation departments. Patients who did not have a diagnosis of CDC/HSC during the review process by the study team, were excluded. The certainty of CDC diagnoses was determined according to the EORTC/MSG criteria for invasive candidiasis [11, 12].

Data Collection

Data were retrieved from the electronic medical record system and laboratory computerized database of each center. Collected variables included: demographic data, hospitalization details, hematological information (medical history and treatment), risk factors for candidiasis (central venous catheterization, antibiotic treatment in the three months prior to CDC, bone marrow transplant and steroid treatment), clinical course and laboratory data, microbiology data (presence of bacteremia during the three months prior to CDC, candidiasis during the two months preceding or following CDC, Cytomegalovirus and invasive aspergillosis), pathology data, Imaging details, antifungal treatment data, and one-year mortality.

Species Identification

During 2005–2011, *Candida* species were identified using CHROMagar Candida (HiLabs, Israel) and API ID 32 C (bioMerieux, France). From 2012 and on, isolates were identified mainly by matrix-assisted laser desorption ionization time.of flight mass spectrometry (MALDi TOF–MS, VITEK MS, bioMerieux, France). Antifungal susceptibility testing was interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for antifungals [17].

Data Analysis

Disease severity was determined according to two variables: (1) Number of organs involved in the disease; (2) Duration of disease. The number of organs involved was determined by imaging findings and disease duration was the period elapsed from clinical diagnosis of CDC to either recovery documented on imaging studies or discontinuation of antifungals, whichever occurred earlier.

Definitions

Proven and probable CDC were defined according to the revised EORTC/MSG definitions of invasive fungal disease [11, 12]. These revised definitions do not include the less reliable definition of possible CDC. Nevertheless, since most patients with hematologic malignancies cannot undergo invasive procedures due to a bleeding risk, we have classified study cases as possible CDC when criteria of a probable diagnosis were met, without the presence of a mycological criterion in accordance with the old 2008 EORTC/MSG definitions [11, 12].

Statistical Analysis

To examine the relationship between two qualitative variables, Chi-square test and Fisher's exact test were used. Comparison of a quantitative variable between two independent groups was done using the non-parametric Mann–Whitney test. A quantitative variable comparison between five independent groups was made using the non-parametric Kruskal–Wallis test with multiple paired comparisons and correction to the level of significance according to Bonferroni. To test the strength of the relationship between two quantitative variables, Spearman's non-parametric correlation coefficient was calculated. Examination both the difference and the agreement between two qualitative dichotomous variables, was done with the McNemar test and the calculation of the Kappa index for the degree of consent beyond chance. ROC analysis was performed to find an optimal cross-sectional point, for a quantitative variable (in terms of sensitivity and specificity), which distinguishes between two categories of disease severity. The non-parametric tests are used due to the small sample size and the abnormal distribution of some of the variables. All statistical tests were bidirectional, and p-value of 0.05 or less was considered statistically significant.

Results

During the study period, 35 patients with CDC diagnosis were included. The median age was 29 (range, 6–67 years). Proven and possible CDC were found in 12 and 23 patients, respectively, according to EORTC/MSG diagnostic criteria [11, 12]. Thirty-

three patients (94%) had an underlying hemato-oncological disorder, one had a kidney transplantation four month prior to CDC, and one had a chronic intestinal pseudo-obstruction with frequent admissions to hospital and total parenteral nutrition (TPN). Other demographic and clinical characteristics are listed in Table 1.

The incidence of CDC in hemato-oncology departments in both centers between years 2005–2019 was 10 patients per 1,000. During the study period, there was a slight upward trend in CDC cases observed in both centers (Fig. 1).

Microbiology and pathology

Overall, microbiological identification of *Candida* was obtained in 16/35 (45.7%) of patients with CDC (11 blood isolates, 9 tissue isolates with 4 overlapping isolates). Identification to the species level was obtained in 12 cases (11 blood isolates, three tissue isolates and 2 overlapping isolates). The most common isolated species was *Candida tropicalis* (n = 8, Table 1) and there were no cases of *Candida albicans*. A biopsy of an involved organ was performed in 21/35 (60%). In 76% of the specimens (16/21), both microbiological and histological evaluation was performed with an almost perfect agreement (8 specimens were positive and 7 negative, in both modalities, kappa coefficient 0.875) (Fig. 2).

Treatment

Eighteen CDC patients (51%) were treated empirically with fluconazole in the three months preceding CDC and such treatment was significantly associated with a prolonged course of disease ($p < 0.05$). There was no association between fluconazole treatment in the three months prior to CDC and fluconazole susceptibility (15 isolates, ($p = 0.57$).

Resolution of CDC and Imaging

Follow-up was performed in most cases by computed tomography (CT) of abdominal organs (71%), with a resolution rate of 33%, 48% and 57%, after 3, 6 and 9 months, respectively, since the initiation of antifungal treatment. The McNemar's test indicated that there was no significant association between clinical resolution according to radiologic findings, and the discontinuation of antifungals, as the *p*-values were all greater than 0.1, at three different times: 3, 6 and 9 months after anti-fungal treatment cessation. The results of the Cohen's kappa test showed moderate to poor agreement between the two measures at the three time points, with κ of 0.2, 0.4, and 0.3, respectively.

Mortality

The one-year mortality of patients with CDC was 9/35 (26%). The most common causes of death were hematologic malignancy (44%) and non-*Candida* related infections (33%).

Severity of CDC and Risk Factors for Severe Disease

The mean number of involved organs was 3 ± 1.26 and the mean disease duration was 178 ± 123 days. No correlation was found between these measures in both distribution curve and Spearman coefficient.

The number of involved organs was positively correlated with fever duration prior to CDC diagnosis ($p = 0.01$), while a negative correlation was found with duration between candidemia onset and CDC diagnosis ($p < 0.05$) (Supplemental Table 1). In univariate analysis, risk factors for severe CDC defined as ≥ 3 organs involvement, were an increased C- Reactive Protein (CRP) level (16.2 mg/dL vs 4.6 mg/dL, $p = 0.05$) and prolonged fever prior to CDC diagnosis (a median of 19 vs 11 days, respectively, $p = 0.034$) (Supplementary Table 1b). A CRP cutoff level of 7.18 mg/dL was found to predict severe disease, with a sensitivity of 80%, specificity of 66.7% and an AUC of 0.8 ($0.57 > 95\%$ CI > 1.0, $p = 0.05$).

CDC duration was positively associated with elevated liver enzymes in the previous two months ($p < 0.03$), and right upper quadrant (RUQ) pain ($p < 0.05$) at diagnosis (Supplementary Table 1a).

When severity of disease was defined as both involvement of ≥ 3 organs and disease duration of > 90 days, severity was positively associated with fever duration prior to CDC diagnosis ($p < 0.05$) and the absence of candidemia in the months prior to or following the diagnosis ($p = 0.05$).

Table 1 Clinical characteristics and outcomes of patients with chronic disseminated candidiasis

Variables	Patients N = 35 (%)
Demographics	
Female	18 (51.4)
Age (median, interquartile range)	29, 15–45
Background characteristics	
Hematological diagnosis[a]	
ALL	13 (37.1)
AML	12 (34.3)
NHL	2 (5.7)
Others[b]	6 (17.1)
Number of chemotherapy protocols (N = 33)	
1	22 (66.7)
2	7 (21.2)
3	3 (9.1)
> 3	1 (3)
Previous bone marrow transplantation	3 (9.1)
Previous bacteremia[c]	21 (60)
Enterobacterales	14 (66.7)
Previous antibiotics[c]	32 (91.4)
Carbapenem	12 (37.5)
CDC course	
Clinical manifestations of CDC	
Fever	32 (91.4)
Respiratory symptoms	15 (42.9)
RUQ pain	11 (31.4)
Liver enzymes abnormalities[d] (N = 33)	24 (72.7)
Hepatocellular abnormalities[d] (N = 29)	13 (44.8)
Cholestatic abnormalitiesd (N = 27)	25 (92.6)
Candidemia event[e]	11 (31.4)
Central venous catheter at candidemia onset	10 (90.9)
Central venous catheter removed during candidemia	6 (60)
Candida species (N = 16)	
Candida tropicalis	8 (50)
Candida dubliniensis	2 (12.5)
Candida glabrata	1 (6.2)
Candida krusei	1 (6.2)
Unknown	4 (25)
Certainty of CDC diagnosis[f]	
Proven	12 (34.3)
Probable	0 (0)
Possible	23 (65.7)
Biopsy of an involved organ	21 (60)
Yeasts in histology	10 (52.6)
Tissue evaluated in microbiology	18 (85.7)
Yeasts in microscopy	5 (27.8)

Table 1 continued

Variables	Patients N = 35 (%)
Candida growth in culture	7 (38.9)
Treatment	
Empirical fluconazole	18 (51.4)
Number of anti-fungal courses	
1	11 (31.4)
2	9 (25.7)
Imaging modality used for follow-up	
CT	25 (71.4)
US	4 (11.4)
[18F]FDG-PET	3 (8.6)
MRI	2 (5.7)
Radiologic resolution after 3 months (N = 27)	9 (33.3)
Radiologic resolution after 6 months (N = 21)	10 (47.6)
Radiologic resolution after 9 months (N = 21)	12 (57.1)
CDC severity	
Number of sites involved (mean ± SD) (N = 34)	2.97 ± 1.267
Days until clinical recovery[g] (mean ± SD) (N = 22)	178.2 ± 122.8
Outcome	
1-year mortality	9 (25.7)
Death cause (N = 9)	
Candida infection	1 (11.1)
Non-Candida infection	3 (33.3)
Hematologic malignancy	4 (44.4)
Unknown	1 (11.1)

ALL; acute lymphoblastic leukemia, AML; acute myeloid leukemia, NHL; non-hodgkin lymphoma, CDC; chronic disseminated candidiasis, RUQ; right upper quadrant, CT; computed tomography, US; ultrasound, [^{18}F]FDG-PET; positron emission tomography with [^{18}F]FDG, MRI; magnetic resonance imaging

[a]Two patients (5.7%) were without any hematological disease

[b]Two cases of aplastic anemia, 1 of Ewing sarcoma, 1 of chronic lymphoblastic leukemia, 1 of malignant histiocytosis and 1 of myelodysplastic syndromes

[c]In 3 months before CDC diagnosis

[d]In 2 weeks before the diagnosis or during the disease

[e]In ± 2 months from CDC diagnosis

[f]According to EORC/MSG criteria

[g]In 13/35 patients there was no information regarding clinical recovery

Discussion

In this study we aimed to characterize clinical features of patients with CDC in two tertiary hospitals in Jerusalem and to define risk factors for severe disease. We have found an increase in CDC incidence over the study years, which cannot be attributed neither to an increase in candidemia events nor a change in prophylactic or empirical anti-fungal protocols, since both were not majorly changed over the years, with an average candidemia incidence of 0.62 cases per 1000 admissions and institutional guidelines recommending prophylaxis with an anti-mold agent in high-risk hematology patients [18]. Our assumption is that the

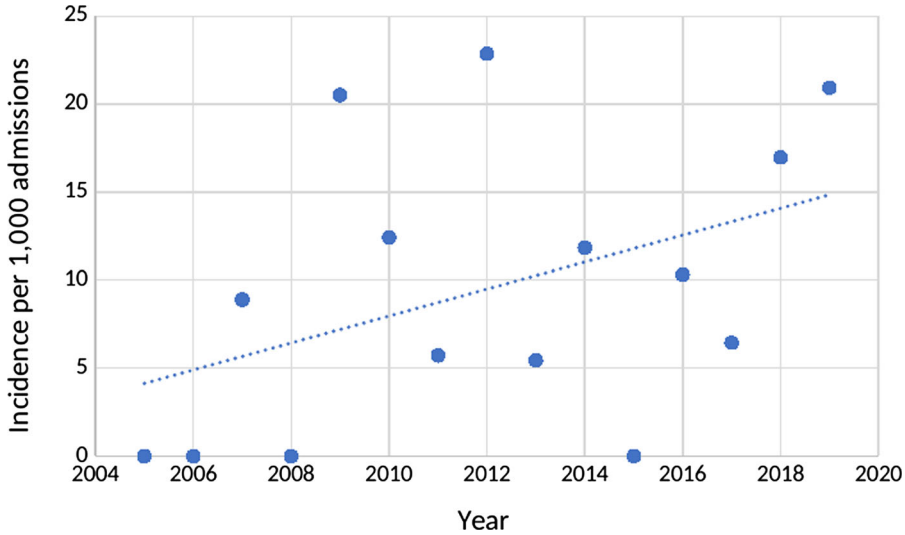

Fig. 1 Chronic disseminated candidiasis incidence in hemato-oncology departments in Jerusalem

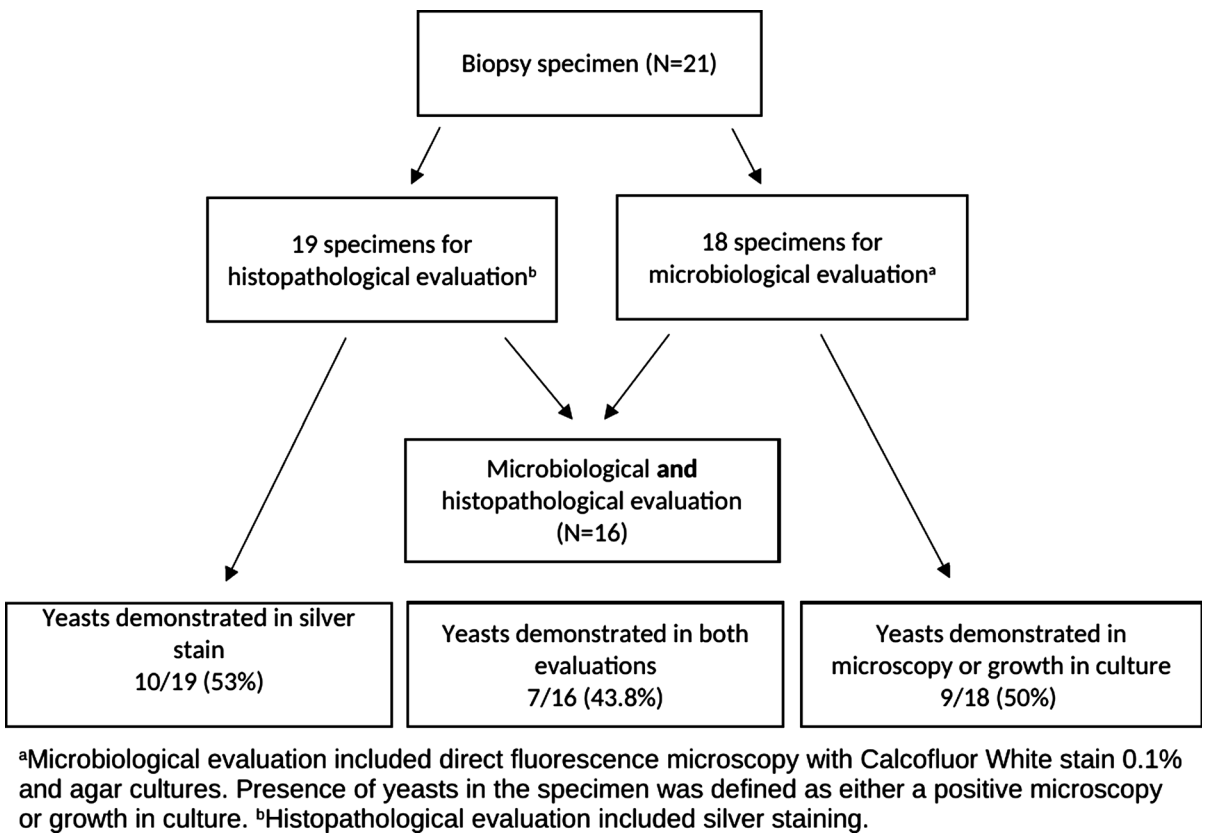

Fig. 2 Histopathological and microbiological evaluation of tissue specimens from patients with CDC

increase in CDC incidence is related to the wide-scale use of more sensitive diagnostic modalities such as CT, Magnetic Resonance Imaging (MRI) and positron emission tomography with [^{18}F]FDG ([^{18}F]FDG-PET), compared to older modalities such as sonography (sensitivity of 57%, 95%, 100% vs 33%, respectively), and to an increased use of broad-spectrum antibiotics [19–21]. Such use impacts gut microbiota and immune system function and is a recognized risk factor for *Candida* colonization in the GI tract and subsequent development of CDC [4, 22]. Indeed, most patients in the study (90%) were treated with antibiotics prior to CDC diagnosis, mostly for *Enterobacterales* bacteremia (Table 1), supporting the presumed pathogenesis of CDC in which an altered gut mucosa is a port of entry for bacteria into the portal bloodstream, leading to portal infection and further dissemination [23, 24].

The clinical presentation of CDC was similar to that described in the previous literature, as most of our patients had fever (91.4%) and a recent elevation in liver enzymes (72.7%) (Table 1) [25]. Similarly, most patients (70%) did not have a preceding or simultaneous candidemia, as previously described, attributed to a low fungal inoculum limited to the portal circulation as well as early treatment with antifungals in neutropenic fever [6, 8, 26]. The one-year mortality rate was similar to mortality rates described formerly [2].

An involvement of more than two organs in former series of CDC is considered to be a rare finding [27]. The average number of involved organs in this study was 3 and we attribute this discrepancy to the utility of sensitive imaging modalities compared to those utilized in the past.

Microbiology and Histopathology

A half of *Candida* species identified in this study (from both blood and involved organs' specimens) were identified as *Candida tropicalis*, and there was no identified case of *C. albicans*, as opposed to published data [13, 14]. In a recent epidemiological study in Jerusalem, it was shown that the most common causative agent of invasive candidiasis in hematological patients is *C. tropicalis* and not *C. albicans*, which is considered the most common cause of invasive candidiasis worldwide [18, 28, 29]. Other studies also identified *C. tropicalis* as the most common *Candida* species colonizing the GI tract and consequently the main causative agent of candidemia in hematological patients [30, 31]. A former study of CDC patients also reported the most common agent as *C. tropicalis* (83% of cases) [30].

Biopsies are not frequently performed in predisposed patients due to the high bleeding risk. In addition, in the majority of cases, *Candida* is not identified in blood. Therefore, most diagnoses are not categorized as proven according to the EORTC/MSG criteria but rather as possible, according to clinical and radiological findings [11, 12]. Although there was a very good agreement between histopathological and microbiological findings in patients that underwent a biopsy (agreement of 15/16 specimens) it is important to examine specimens simultaneously by both methods to improve diagnostic accuracy.

Imaging Modalities

Fifty-seven percent of the patients continued to have visible lesions 9 months after starting antifungals and the main follow up modality was CT. According to the Infectious Diseases Society of America (IDSA), current practice guidelines recommend continuing antifungals until the lesions resolve, as demonstrated by repeat imaging, in order to prevent relapse, which may take several months [4]. A former study that evaluated residual lesions of CDC (among other invasive fungal infections) found [^{18}F] FDG-PET to be a sensitive tool to evaluate clearance of lesions and demonstrated a decrease or disappearance in uptake at the site of infection several weeks preceding the scarring in CT or MRI [32, 33]. This suggests that FDG-PET can be useful in helping to stop antifungals earlier.

Clinical resolution of CDC according to physicians' assessment did not associate with radiological recovery as determined by imaging studies, implying that duration of antifungal treatment for CDC may be longer than necessary. This finding also emphasizes the importance of follow up with sensitive imaging modalities.

Risk Factors for Severe Disease

The main risk factors for severe disease, manifested by the number of involved organs, were prolonged fever and short candidemia prior to CDC diagnosis. In

univariate analysis, when severe disease was defined as involvement of ≥ 3 organs, the main risk factors were prolonged fever prior to CDC and increased CRP at CDC diagnosis. The latter is a known marker for CDC signifying an inflammatory involvement [34]. We found a cutoff level of 7.18 mg/dL to be a possible predictor of ≥ 3 organ involvement although this finding is based on 16 observations only and should be further validated. The correlation of severe disease with prolonged fever before diagnosis underlines the importance of timely diagnosis and treatment to avoid organ seeding, whereas cases of CDC associated with short candidemia should prompt a search for organ dissemination since they signify a high circulating *Candida* inoculum. Elevated liver enzymes in the preceding months as well as the presence of RUQ pain at CDC diagnosis are possible manifestations of prolonged disease, perhaps secondary to marked liver seeding. The absence of candidemia around CDC diagnosis was associated with a longer course and organ dissemination, possibly because the presence of candidemia prompts early treatment.

The main limitation of the study is its retrospective nature and the relatively small group of patients. Therefore, validation of these findings is required in larger cohorts. Additionally, the evaluation of CDC severity according to disease duration, as determined by clinical decision or radiological recovery, may be inaccurate since no association was found between the two.

In conclusion, as opposed to other studies, we found CDC to be associated with marked organ involvement, possibly as a consequence of improved imaging modalities, with *Candida tropicalis* being the most common causative agent. Factors as prolonged fever before CDC diagnosis, absence of candidemia and a high CRP level may predict disease severity and assist in treatment decisions and follow-up planning.

Author contributions MK, NC and EO-H contributed to the study conception, methodology, investigation and design. Material preparation, data collection and analysis were performed by NC. Supervision was performed by MK, EO-H and TL. The first draft of the manuscript was written by NC, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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