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The diagnostic sensitivity of beta-D-glucan assay in patients with chronic disseminated candidiasis

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Abstract

Objectives: Chronic disseminated candidiasis (CDC) is a specific syndrome in patients with hematologic malignancies which usually occurs after the recovery of neutrophils due to previous chemotherapy. The beta-D-glucan (BDG) assay has been proposed as an adjunct test for diagnosing invasive fungal infection. However, data on BDG assay in patients with CDC are scarce. We aimed to investigate the diagnostic sensitivity of BDG assay in patients with CDC.

Methods: All adult patients who were diagnosed as CDC in a tertiary hospital in Seoul, South Korea, from January 2017 to December 2019 and underwent BDG assay (Gold Mountain River Tech Development, Beijing, China) were retrospectively reviewed. CDC was defined by the demonstration of small, target-like abscesses in the liver or spleen (bull's-eye lesions) or in the brain at the time of neutrophil recovery after a prolonged phase of neutropenia. The values for BDG over 80 pg/mL were classified as positive.

Results: A total of 20 patients were enrolled. The median age was 51 years (IQR 39 – 64). Of these, 13 patients had AML, 3 ALL, 2 MDS, and 1 aplastic anemia. *Candida* spp. were isolated in 6 patients; 3 were *C. tropicalis*, 2 *C. glabrata*, and 1 *C. krusei*. Of the 20 patients, 10 (50%) revealed positive BDG results. The median BDG value was 174 pg/dL (IQR 137–402). More CDC patients with previous candidemia had positive BDG assay than those without candidemia, but with no statistical significance (4/5 (80%) vs. 6/15 (40%), $P = 0.30$). In the 7 patients with BDG assay-positive CDC, for whom follow-up BDG results were available, the BDG remained high in 6 patients (86%) for more than 4 weeks after adequate antifungal therapy. All 4 patients who died had a positive BDG assay, and 3 of them showed an increasing trend of BDG values during treatment.

Conclusions: Negative BDG assay appears to be not useful to rule out CDC. BDG assay decreased slowly during the adequate treatment of CDC.

Introduction

Chronic disseminated candidiasis (CDC) is a unique syndrome in patients with hematologic malignancy. The disease usually develops during the recovery of neutrophils after intensive chemotherapy. It is characterized by organ involvement, mainly the liver and the spleen [1]. The diagnosis of CDC is very challenging. Diagnostic criteria for proven CDC require obtaining positive cultures for Candida spp. in blood or a sterile tissue specimen [2]. However, not only the sensitivity of culture tests is low, but also obtaining tissue through invasive procedures in critically ill patients with suspected CDC is not always feasible [1,3,4]. For such reasons, there has been a demand for non-invasive diagnostic tests for CDC.

The serum β-d-glucan (BDG) assay is a non-invasive test for circulating cell wall components of fungus [5]. Diagnostic performance of BDG varies among different fungal infections and different patient population [6-9]. Growing evidence supports the utility of BDG for the diagnosis of invasive candidiasis and PCP [2,10]. However, little is known about the diagnostic performance of BDG in patients with CDC. Furthermore, its kinetics in the course of antifungal treatment is rarely investigated. Therefore, in this study, we aimed to investigate the diagnostic sensitivity and kinetics of BDG assay in patients with CDC.

Materials and Methods

Study population and definitions

All eligible adult patients who were diagnosed as CDC in a tertiary hospital in Seoul, South Korea, from January 2017 to December 2019 and underwent BDG assay (Gold Mountain River Tech Development, Beijing, China) were retrospectively reviewed.

Definition of CDC and positive BDG assay

CDC was defined according to the criteria established by the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG). Cases were considered to be "proven" if histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained from liver tissue revealed yeast infection with pseudohyphae or true hyphae or if liver biopsy specimens gave positive culture results showing a clinical or radiological abnormality consistent with infection. Cases were classified as "possible" if the patients with relevant host factors such as hematologic malignancies yielded small, target-like abscesses in the liver or spleen (bull's-eye lesions) or the brain at the time of neutrophil recovery after a prolonged phase of neutropenia. The values of BDG assay (Gold Mountain River Tech Development, Beijing, China) above 80 pg/mL were classified as positive.

Results

Patient characteristics

A total of 20 patients with CDC were enrolled. Table 1 shows a comparison of the baseline characteristics and treatment outcomes of BDG-positive and BDG-negative patients with CDC. The median age was 51 years (IQR 39 – 64). Of these, 13 patients had acute myeloid leukemia, 3 had acute lymphoblastic leukemia, 2 had myelodysplastic syndrome, and 1 had aplastic anemia. Two cases were proven CDC confirmed by liver biopsy. Of the six patients with the growth of candida species in blood or biopsied tissue culture, C. tropicalis were isolated in 3 patients, C. glabrata were isolated in 2 patients, and C. krusei was isolated in one patient. A total of 10 (50%) revealed positive BDG results. The median BDG value was 174 pg/dL (IQR 137–402). Candida organ involvements were most commonly observed in the liver (80%) and spleen (35%) followed by the brain, lung, and skin (10%).

Kinetics of BDG in patients with CDC

In the 7 patients with BDG assay-positive CDC, for whom follow-up BDG results were available, the BDG remained high in 6 patients (86%) for more than 4 weeks after adequate antifungal therapy. All 4 patients who died within 90 days of CDC diagnosis had a positive BDG assay, and 3 of them showed an increasing trend of BDG values during treatment. In the 8 patients with BDG assay-negative CDC, BDG levels of 7 patients remained negative for 4–6 weeks. (Fivure 1, 2)

Table 1. Clinical characteristics in patients with chronic disseminated candidiasis

	Total (n = 20)	BDG positive (n = 10)	BDG negative (n = 10)	P value
Age, median years (IQR)	51 (39 –64)	47 (30–66)	51 (48–55)	0.83
Male sex	12 (56)	7 (70)	5 (50)	0.65
Underlying disease				
Acute myeloid leukemia	13 (65)	6 (60)	7 (70)	> 0.99
Acute lymphocytic leukemia	3 (15)	2 (20)	1 (10)	> 0.99
Myelodysplastic syndrome	2 (10)	1 (10)	1 (10)	> 0.99
Aplastic anemia	1 (5)	1 (10)	0 (0)	> 0.99
Mixed phenotype acute leukemia	1 (5)	0 (0)	1 (10)	> 0.99
Positive serum galactomannan antigen test	3 (15)	3 (30)	0 (0)	0.21
Proven CDC	2 (10)	1 (10)	1 (10)	> 0.99
Proven candida species (from biopsied specimen or blood culture)	6 (30)	5 (50)	1 (10)	0.14
CDC location				
Liver	16 (80)	7 (70)	9 (90)	0.58
Spleen	7 (35)	2 (20)	5 (50)	0.35
Brain	2 (10)	2 (20)	0 (0)	0.47
Lung	2 (10)	2 (20)	0 (0)	0.47
Skin	2 (10)	2 (20)	0 (0)	0.47
Kidney	1 (5)	1 (10)	0 (0)	> 0.99
Candida species				
C. albicans	1 (5)	1 (10)	0 (0)	> 0.99
C. tropicalis	4 (20)	3 (30)	1 (10)	0.58
C. parapsilosis	0 (0)	0 (0)	0 (0)	> 0.99
C. glabrata	1 (5)	1 (10)	0 (0)	> 0.99
C. krusei	0 (0)	0 (0)	0 (0)	> 0.99
Not identified	14 (70)	5 (50)	9 (90)	0.14
Prior allogenic stem cell transplantation	5 (25)	2 (20)	3 (30)	> 0.99
Duration of neutropenia >2 weeks	13 (65)	8 (80)	5 (50)	0.35
Received prophylactic antifungal agent	4 (20)	3 (30)	1 (10)	0.58
Median duration of treatment, days (IQR)	110 (60–195)	70 (47–120)	170 (93–203)	0.29
Antifungal therapy				
Fluconazole	16 (80)	6 (60)	10 (100)	0.09
Polyenes	3 (15)	3 (30)	0 (0)	0.21
Echinocandins	4 (20)	2 (20)	2 (20)	> 0.99
Voriconazole	1 (5)	1 (10)	0 (0)	> 0.99
90-day mortality	4 (20)	4 (40)	0 (0)	0.09

Figure 1. Kinetics of β-D-glucan levels in patients with chronic disseminated candidiasis who had positive β-D-glucan levels at the time of diagnosis

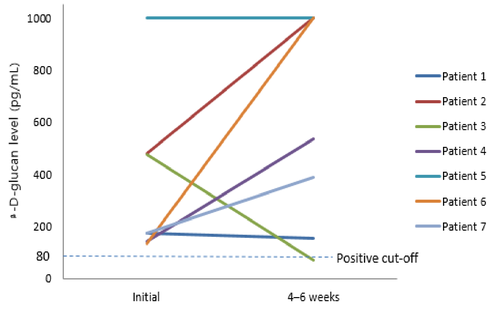
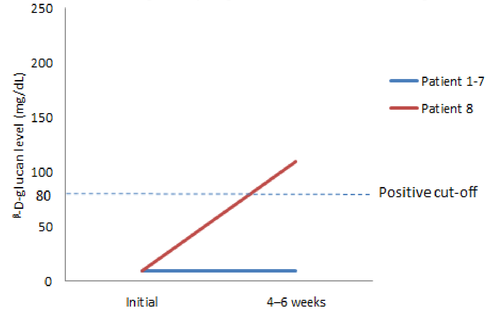


Figure 2. Kinetics of β-D-glucan levels in patients with chronic disseminated candidiasis who had negativee β-D-glucan levels at the time of diagnosis



Discussion

CDC, which mainly occurs in patients with hematological malignancy, is difficult to diagnose [4]. Culture-based methods are insensitive, and invasive procedures are not always feasible [1,3,4]. For this reason, there were expectations for the usefulness of the serum BDG assay, a non-invasive test, in the diagnosis of CDC, but little was known about it [11,12]. In our study, the sensitivity of BDG to CDC diagnosis was not as high as 50%. Although it has been previously reported that BDG is useful for the evaluation of deep-seated infection, it has limitations in only a very small number of CDCs (less than 10 adult patients) [12,13]. Based on our study, it seems that CDC cannot be ruled out even if BDG is negative if clinically suspected.

In previous studies on invasive candidiasis, it is known that the clinical outcome is better when BDG decreases after treatment or when BDG at diagnosis is consistently negative [14]. Also, one study reported that a slow decrease in BDG after candidemia was associated with deep seated candidiasis [13]. For CDC, one of the invasive candidiasis, only one study reported the kinetics of BDG during treatment [12]. Nine CDC with favorable outcome showed a tendency to decrease in BDG, and two CDC with fatal outcome showed consistently high BDG values [12]. This is a result similar to our study. All 4 patients who died in this study had positive BDG values at the time of diagnosis, and 3 of them showed a trend of increasing BDG levels until 4-6 weeks after diagnosis. Even in 4 patients who recovered properly, if BDG was positive at the time of diagnosis, it continued to be positive after 4-6 weeks. All patients with negative BDG level at diagnosis survived after 90 days, and only one of them had positive BDG, which is considered a may be false positive. Based on our study, BDG level tends to decrease slowly after CDC treatment, and if it is persistently negative, it may be associated with good clinical outcome.

Our study has several limitations. First, as a retrospective study, BDG assay was performed according to the clinician's judgment, so there was no regular follow-up during the treatment process. Second, only 20 CDC patients were included. However, CDC is a rare disease, and in particular, it was a study with the largest number of patients dealing with the relationship between this disease and BDG assay. Although there are limitations, this study will be an invaluable reference for CDC practice in clinical practice.

Conclusion

Negative BDG assay appears to be not useful to rule out CDC. BDG assay decreased slowly during the adequate treatment of CDC.

Reference

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