

NON-NEOFORMANS CRYPTOCOCCEMIA IN A PATIENT WITH HODGKIN'S LYMPHOMACHUAN HUN DING^{1*}, NORHIDAYAH KAMARUDIN²¹Department of Medical Microbiology and Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.²Department of Pathology and Laboratory Medicine, Kulliyah of Medicine, International Islamic University Malaysia, Kuantan Campus, Pahang, Malaysia. Email: dingch@ppukm.ukm.edu.my

Received: 19 September 2018, Revised and Accepted: 19 October 2018

ABSTRACT

Cryptococemia attributed to non-neoformans cryptococci has not received much attention due to the relative scarcity of reported cases. The primary aim of this case report is to highlight several notable characteristics of *Cryptococcus laurentii*. A 35-year-old woman presented with a right supraclavicular mass and a history of low-grade fever. A yeast was isolated from her blood. It formed cream-colored colonies which turned yellowish after 72 h of incubation and had a microscopic morphology of elongated budding yeast cells. Its identity was confirmed to be *C. laurentii* through carbohydrate assimilation testing (ID 32 C). The patient responded clinically to fluconazole and cleared the cryptococemia. She was subsequently diagnosed with Hodgkin's lymphoma through histopathological examination of the supraclavicular mass.

Keywords: *Cryptococcus laurentii*, Fluconazole, Hodgkin's lymphoma.

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INTRODUCTION

Non-neoformans cryptococci are generally regarded as non-pathogenic saprophytes [1,2]. Moreover, it has also been established that *Cryptococcus laurentii* (a non-neoformans *Cryptococcus* species) is less virulent than *Cryptococcus neoformans* [3]. However, as the number of immunocompromised patients increases, so must the recognition that non-neoformans cryptococci can become clinically important human pathogens [4]. Although non-neoformans cryptococci can also cause serious infections (e.g., central nervous system and bloodstream infections), the clinical manifestations are often indistinguishable from those attributable to *C. neoformans* [5]. *C. laurentii* has been reported to have reduced susceptibility to fluconazole [5], a commonly prescribed antifungal agent which may be employed to treat *C. neoformans* infections. This case report highlights some notable characteristics of *C. laurentii* which may be important for diagnostic and clinical purposes.

CASE REPORT

A 35-year-old woman presented to a tertiary medical center for investigation of a right supraclavicular mass. The mass was initially a painless and thumb-sized swelling when it was first noticed by the patient 5 months back. Subsequently, the mass progressively increased in size and became painful. The local symptoms were also associated with low-grade fever. On examination, the patient was fully conscious, not tachypneic but febrile with a body temperature of 37.6°C. A large swelling was noted at her right supraclavicular region, measuring 20×15 cm. A sinus was seen to discharge hemerosous fluid. The mass was firm and fixed to the overlying skin. No other neck masses or lymph nodes were palpable. Examination of respiratory, cardiovascular, and other systems was unremarkable. A provisional diagnosis of staphylococcal supraclavicular abscess was made and she was empirically treated with intravenous cloxacillin 500 mg q6h.

Preliminary laboratory investigations of the patient's blood revealed leukocytosis (total white cell count of 21.8×10^9 cells/L) with evidence of neutrophilia (18.1×10^9 cells/L) and a raised C-reactive protein level (9.22 mg/dL). Her retroviral screening was non-reactive. A swab of the discharge and a blood specimen were sent for microbiological culture.

The supraclavicular mass was also biopsied for histopathological examination. After 4 days of incubation, the blood specimen in the BACTEC Myco/F Lytic vial was positive for microbial growth. A Gram stain revealed elongated and budding yeast cells with no pseudohyphae. The yeast was cultured on Sabouraud dextrose agar (SDA) and cream-colored colonies were observed after 48 h of incubation at 35°C, which turned yellowish after 72 h. On cornmeal agar, elongated and budding yeast cells were observed under the light microscope (Fig. 1). Through carbohydrate assimilation tests (ID 32 C; bioMerieux, France), the yeast was finally identified as *C. laurentii* (numerical profile: 5777377371, 99.0% identification). The swab specimen grew coagulase-negative staphylococci and the bacteria were regarded as skin contaminants.

Following the release of the blood culture report, intravenous cloxacillin was discontinued after 6 days and a course of intravenous fluconazole 400 mg OD was started. A follow-up blood culture after a week of fluconazole treatment was negative for both bacteria and fungi. The patient responded clinically to the antifungal therapy and was allowed home after completing a 2-week course of fluconazole. Two weeks post-admission, the histopathological report for the supraclavicular mass (lymph node) provided a diagnosis of classical Hodgkin's lymphoma. Fungal stains (i.e., periodic acid-Schiff and Grocott-Gomori methenamine silver) did not reveal the presence of any fungal elements/bodies in the tissue specimen.

DISCUSSION

Non-neoformans cryptococci are encapsulated yeasts with a worldwide prevalence and they can be isolated from numerous environmental sources and foods [5]. The term "non-neoformans cryptococci" traditionally refers to *Cryptococcus* spp. other than *C. neoformans* and *Cryptococcus gattii* because the latter was previously considered a variant of *C. neoformans* [4]. Approximately 80% of non-neoformans cryptococcal infections are caused by *C. laurentii* and *Cryptococcus albidus* [4]. Most cases of non-neoformans cryptococcal fungemia are nosocomially acquired and the presence of invasive devices is a significant predisposing factor particularly when associated with *C. laurentii* infections [6]. Although in the present case, the patient did not have any indwelling medical device (e.g., central venous line), by having a hematological

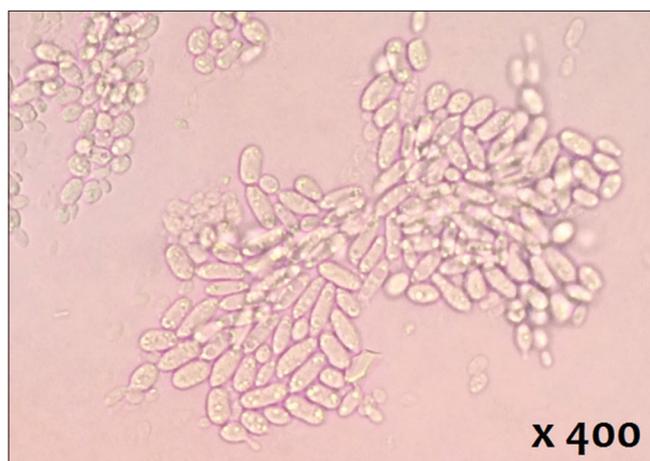


Fig. 1: Microscopic morphology of *Cryptococcus laurentii* cultured on cornmeal agar

malignancy (i.e., lymphoma), her cell-mediated immunity could have been compromised, leading to the *C. laurentii* cryptococemia [4]. Although *C. laurentii* fungemia has been reported before in patients with underlying non-Hodgkin's lymphoma [4,7], to the best of our knowledge, there has been no report associating the infection with classical Hodgkin's disease.

Although *C. laurentii* is India Ink positive and produces urease, these characteristics are common to all cryptococci. However, the capsule of *C. laurentii* in the India Ink mount is narrow/slight [1,8]. Furthermore, its microscopic morphology is that of elongated and budding yeast cells [9] rather than the globose yeast cells which are more typical of *C. neoformans* and *C. gattii*. Another clue to the presence of *C. laurentii* is yellow (or orange) colonies on SDA, especially after extended incubation [10]. A negative caffeic acid test is another supplementary test which would distinguish *C. laurentii* from *C. neoformans* [8]. Non-*neoformans* cryptococci are less likely to produce positive results in cryptococcal antigen detection tests [4], and thus, glucuronoxylomannan antigen assays should not be relied on to diagnose cases of *C. laurentii* fungemia. For laboratories without molecular identification (i.e., DNA sequencing) capabilities, commercial carbohydrate assimilation kits for yeasts such as ID 32 C (bioMérieux, France) may be utilized [8].

There are no established guidelines for the treatment of infections caused by *C. laurentii* [9,10]. However, with regard to the *in vitro* susceptibility profile of *C. laurentii*, a study on 39 isolates revealed that amphotericin B was the most active compound, fluconazole had limited activity, and flucytosine as well as echinocandins were inactive [2]. In contrast, fluconazole resistance has been virtually absent in *C. neoformans* isolates from Asia [11]. Admittedly, we did not perform antifungal susceptibility testing on our *C. laurentii* isolate because there were no published Clinical and Laboratory Standards Institute breakpoints for the antifungal susceptibility testing of cryptococci. We were, however, fortunate that our patient responded clinically to fluconazole. Other authors have also reported positive outcomes with fluconazole therapy, either as a sole therapeutic agent [9] or as a subsequent antifungal agent following amphotericin B therapy [1]. Other azoles (e.g., voriconazole) were also used successfully to treat infections caused by *C. laurentii* [10]. The recent discovery of new antifungal compounds from plants such as fenugreek and clove basil could also potentially expand the antifungal arsenal against *C. laurentii* [12,13].

CONCLUSION

All clinical microbiology laboratories should attempt to identify non-*neoformans* cryptococci to the species level to aid therapeutic decisions. Due to the unpredictable fluconazole susceptibility profile, the threshold to switch to amphotericin B should be low for patients with *C. laurentii* infections who are initially managed with fluconazole.

ACKNOWLEDGMENT

We would like to thank the Dean of the Faculty of Medicine, Universiti Kebangsaan Malaysia, for her motivation and permission to publish this article. We are also grateful for the technical assistance provided by Prof. Dr. Srijit Das from the Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia.

AUTHOR'S CONTRIBUTIONS

Study conception and design: Chuan Hun Ding. Collection and data analysis: Norhidayah Kamarudin. Drafting of article and revising it critically for important intellectual content: Chuan Hun Ding and Norhidayah Kamarudin. Final approval of the version to be submitted: Chuan Hun Ding and Norhidayah Kamarudin.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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