CASE REPORT

Case Series of *Kodamaea ohmeri*: An Emerging Fungal Infection in Srinagarind Hospital, Thailand

Natapong Manomaiwong, MD[1], Waewta Kuwatjanakul, BSc[2], Atibordee Meesing, MD[1,3], Kittipan Samerpitak, PhD[4], Lumyai Wonglakorn, MSc[2], Wantin Sribenjalux, MD[1,3]

[1] Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[2] Microbiology Unit, Clinical Laboratory Section, Srinagarind Hospital Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[3] Research and Diagnostic Center for Emerging Infectious Diseases (RCEID), Khon Kaen University, Thailand

[4] Department of Microbiology, Faculty of Medicine, Khon Kaen University, Thailand

Kodamaea ohmeri, a yeast species within the Saccharomycetaceae family, has been an emerging pathogen in recent decades, leading to an increasing number of human infections, particularly in immunocompromised patients. Fungemia caused by *K. ohmeri* is associated with a high mortality rate of 31%. The present study presents three cases of *K. ohmeri* infections at Srinagarind Hospital, involving children and the elderly with comorbidities such as essential hypertension, diabetes, or neutropenia. These patients underwent surgeries, experienced complications necessitating antibiotic administration, and most received central venous catheterization. Subsequently, they developed new-onset high fever, *K. ohmeri* was identified in hemocultures, and antifungal treatment was initiated. Notably, there are currently no recommended treatments, and no reported cases of *K. ohmeri* infection in Thailand have been documented to date. This case series emphasizes the exploration of infection risks and treatment considerations for further study.

Keywords: *Kodamaea ohmeri*; Emerging pathogen; Fungemia; Thailand

Received 31 January 2024 | Revised 25 March 2024 | Accepted 15 July 2024

J Med Assoc Thai 2024;107(Suppl.1):S147-51

Website: http://www.jmatonline.com

Kodamaea ohmeri formerly designated as *Yamadazyma ohmeri*, represents a yeast species within the Saccharomycetaceae family[1]. It inhabits various environments and is distinguished for its significant role in fermentation within the food industry[2]. Over the past few decades, *K. ohmeri* has emerged as a pathogenic organism, evidenced by a growing number of human infections, particularly in immunocompromised patients, leading to conditions such as fungemia, endocarditis, pneumonia, peritonitis, urinary tract infection, and cellulitis[3-7]. The associated mortality rate was reported at 31%[8]. The absence of a comprehensive understanding of *K. ohmeri* infection has hindered the establishment of standardized treatment recommendations. It is noteworthy that, to date, there have been no reported cases of *K. ohmeri* infection in Thailand. The authors aimed to present a case series of *K. ohmeri* infections at Srinagarind Hospital, a 1,500-bed university hospital located in the Khon Kaen district of Northeastern Thailand. The focus was on aspects such as infection risks and clinical syndromes for further study.

Correspondence to:

Sribenjalux W.

Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-43-363746, +66-43-363664

Email: wantsr@kku.ac.th

How to cite this article:

Manomaiwong N, Kuwatjanakul W, Meesing A, Samerpitak K, Wonglakorn L, Sribenjalux W. Case Series of *Kodamaea ohmeri*: An Emerging Fungal Infection in Srinagarind Hospital, Thailand J Med Assoc Thai 2024;107(Suppl.1):S147-51

DOI: 10.35755/Jmedassocthai.2024.S01.S147-S151

Case Report

Case description

The authors have documented three cases of *K. ohmeri* infection at Srinagarind Hospital between the year 2022 and 2023.

Case 1: A 64-year-old male, with underlying essential hypertension (HT) and rectal stenosis, manifested an enterocutaneous fistula (ECF) following surgery. Subsequently, he was transferred to the hospital for further operative intervention.

Case 2: A 5-year-old male, with underlying G-6-PD deficiency and congenital cyclic neutropenia, was diagnosed with a severe soft tissue infection. He was transferred to the hospital for surgical treatment, and during the course of admission, he developed septic shock from an ECF, necessitating central venous catheterization.

Case 3: A 78-year-old female, with underlying poorly controlled diabetes mellitus (DM), HT, single-vessel disease (SVD), and symptomatic severe aortic stenosis,

was admitted for elective coronary artery bypass graft (CABG) surgery and aortic valve replacement (AVR). Post-operation, she experienced gastrointestinal bleeding with hemorrhagic shock and subsequently underwent central venous catheterization.

Despite variations in age, principal diagnoses, and comorbidities among these cases, commonalities exist, such as a postoperative period, prior exposure to broad-spectrum antibiotics, hospital stays exceeding one month, and the development of fungemia. Their respective details are comprehensively outlined in Table 1.

Under consideration of case 2, the male patient was diagnosed with congenital cyclic neutropenia, characterized by periodic absolute neutrophil count (ANC) fluctuations and severe neutropenia episodes every two to three weeks[9]. Despite the administration of Granulocyte Colony-Stimulating Factor (G-CSF) at a dosage of 5 mcg/kg/day, the patient continued to exhibit symptoms of cyclic neutropenia. Subsequently, he developed a catheter-related bloodstream infection (CRBSI) attributed to *K. ohmeri*. Following the removal of the central venous catheter and the initiation of a combination antifungal regimen, he endured a prolonged duration of fungemia lasting 78 days. Endophthalmitis and infective endocarditis were ruled out by thorough evaluation under supervision of an ophthalmologist and a cardiologist. Concurrently, *K. ohmeri* was not detected in cultures from various other sites, including wounds on the buttock, ascitic fluid, sputum, and urine. Subsequently, it was discovered that the patient had a thrombus in the internal jugular vein, where the infected catheter had been inserted, which was considered the focus of the *K. ohmeri* infection. Thus, anticoagulant therapy was prescribed for at least 12 weeks. Following clot resolution, fungal clearance from the bloodstream was confirmed.

Microbiological study

The blood culture bottles of each patient were collectively placed in the automated incubators, at 35°C, typically within a 48-hour, upon the detection of positive result. This procedure mirrored the technique used for

Table 1. Major characteristics of the patients infected by *K. ohmeri* at Srinagarind Hospital between the year 2022 and 2023

	Case 1	Case 2	Case 3
Sex	Male	Male	Female
Age (years)	64	5	78
Principle diagnosis	cIAI	Gas gangrene right buttock	SVD with severe AS
Comorbidities	HT, rectal stenosis s/p loop colostomy with ECF	Cyclic neutropenia, G-6-PD deficiency, ECF	Poorly-controlled DM, HT
Exposed ATB before infection	Ceftriaxone, metronidazole, and meropenem	Meropenem, vancomycin, and amikacin	Meropenem, and vancomycin
Signs and symptoms	Fever with chills	Septic shock	Septic shock
LOS before infection (days)	35	54	64
Site of infection	Fungemia	CRBSI	CRBSI
Strain number of isolated *K. ohmeri*	B-CND-019	B-CND-020	B-CND-030
Drug susceptibility (MIC, µg/dL)	Amphotericin B (0.5)	Amphotericin B (0.5)	Amphotericin B (<0.12)
	Anidulafungin (0.25)	Anidulafungin (0.25)	Anidulafungin (0.12)
	Caspofungin (1)	Caspofungin (0.12)	Caspofungin (0.03)
	Fluconazole (8)	Fluconazole (4)	Fluconazole (4)
	Flucytosine (<=0.06)	Flucytosine (<=0.06)	Flucytosine (<=0.06)
	Itraconazole (0.25)	Itraconazole (0.12)	Itraconazole (0.06)
	Micafungin (0.12)	Micafungin (0.12)	Micafungin (0.03)
	Posaconazole (0.12)	Posaconazole (0.12)	Posaconazole (0.03)
	Voriconazole (0.06)	Voriconazole (0.03)	Voriconazole (0.03)
Treatment	Fluconazole 12 MKD for 14 days	Amphotericin B 1 MKD plus fluconazole 12 MKD for 8 days then micafungin 3 MKD plus fluconazole 12 MKD for 43 days then fluconazole 12 MKD for 55 days	Amphotericin B 1 MKD for 9 days then fluconazole 12 MKD for 6 days
Duration of fungemia after antifungal therapy initiation (days)	0	78	4
Status in the visit	Alive	Alive	Dead

AS=aortic stenosis; cIAI=complicated intra-abdominal infection; CRBSI=catheter-related bloodstream infection; ECF=enterocutaneous fistula; HT=hypertension; LOS=length of stay; MIC=minimum inhibitory concentration; MKD=milligram/kilogram/day; s/p=status-post; SVD=single vessel disease

routine bacterial blood culture and did not necessitate special bottles for fungus. The sample from a positive bottle was sub-cultured on media such as blood agar, MacConkey agar, and chocolate agar, and concurrently conducted for gram staining. The samples from three positive bottles showed numerous yeast cells by the staining. After the incubation for 18 to 24 hours, the yeast colonies appeared on blood agar and chocolate agar those inoculated with a sample of each yeast-positive bottle. The three yeast strains isolated from the three patients were identified as *Kodamaea ohmeri* by Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) (MALDI Biotyper®, Bruker, Germany) with the low-confidence scores of 1.91, 1.81 and 1.79, and assigned the number of each strain as B-CND-019, B-CND-020 and B-CND-030, respectively. The three strains were confirmedly identified as *K. ohmeri* by molecular method using DNA sequence of internal transcribed spacer (ITS) region and phylogenetic analysis as shown in Figure 1.

The three yeast strains and *Candida krusei* ATCC 6258, a reference-control strain, were performed antifungal susceptibility testing (AST) by using the Sensititre YeastOne YO10 AST kit employing the broth microdilution (BMD) technique (Thermo ScientificTM Inc., UK). The kit is approved by the U.S. Food and Drug Administration (FDA) and includes amphotericin B, anidulafungin, caspofungin, fluconazole, flucytosine, itraconazole, micafungin, posaconazole, and voriconazole. The reference strain, *C. krusei* ATCC 6258, showed the accepted minimum inhibitory concentrations (MIC) values. It is noteworthy that either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has not established standard breakpoint for *K. ohmeri*. When compare to the breakpoints of *Candida* spp.[10], three *K. ohmeri* strains appeared to be sensitive to amphotericin B, flucytosine, echinocandins, as well as the new generation of triazoles such as voriconazole and posaconazole. However, they tended to show an elevated MIC to fluconazole.

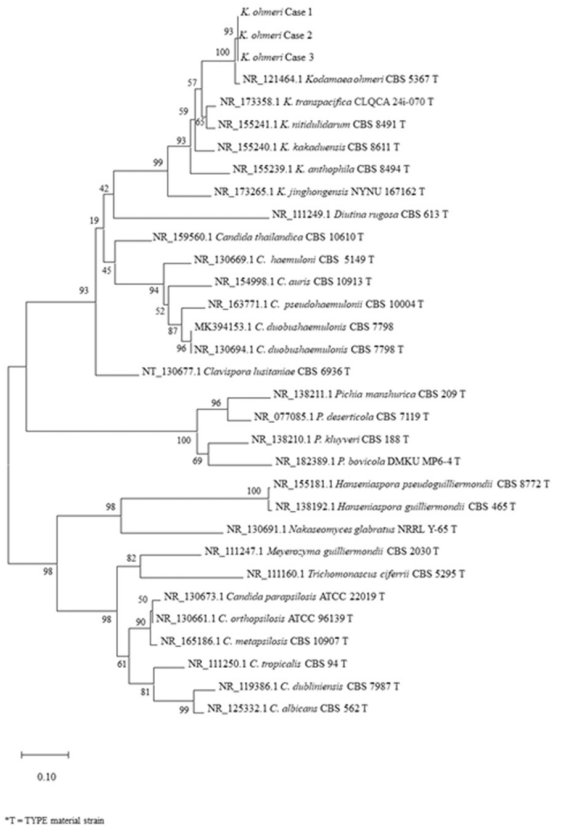

Figure 1. Phylogenetic tree based on ITS sequences of K. ohmeri and other yeast strains. The tree was analyzed by Neighbor-joining method with 1,000 bootstrap replications.

Discussion

Historically, *K. ohmeri* has been predominantly thought to inhabit environmental niches and has been utilized in fermentation processes[2]. However, limited research indicates that it constitutes a minor component among oral commensal non-*Candida* yeasts[11,12] and gut microbiota of human[13]. Additionally, it is found in the skin and nails of patients who have developed phlebitis or subcutaneous infections attributed to this organism[8]. This implies that pathogenesis of *K. ohmeri* infection can be categorized into two major modes, depending on the routes of acquisition: exogenous and endogenous. In cases of exogenous infection, like finger cellulitis resulting from a prick by a thorn[14], we observe a strong connection between compromised immune systems and the onset of infection. Factors such as advanced age or the presence of comorbidities like solid and hematologic malignancy, diabetes, end-stage renal disease, and the use of immunosuppressive agents or corticosteroids have been identified as contributors to the infection. These conditions undermine the body's protective phagocyte-dependent antifungal responses[15]. Interestingly, instances of *K. ohmeri* in patients with immunocompetent status are rarely reported[16].

When assessing the route of infection, case 1 appears to be consistent with an endogenous infection, supported by the presence of developing enterocutaneous fistulas that facilitate the translocation of the fungus from the gastrointestinal tract to the bloodstream. In contrast, case 2 also displays enterocutaneous fistulas and experiences a neutropenic episode during fungemia. However, meeting the criteria for CRBSI suggests that the punctured skin might serve as a potential entry point. While CRBSI due to *Candida* spp. is typically associated with endogenous skin

flora, it's worth noting that exogenous transmission from the hands of healthcare personnel is well-documented[17]. Consequently, determining the route of infection in cases 2 and 3 remains inconclusive. In concordance with prior reports, it is indicated that a majority of individuals afflicted with *K. ohmeri* infections are of extreme age (children or the elderly) or have an immunocompromised status. Additionally, these patients commonly undergo invasive medical procedures, develop clinical manifestations of septic shock with fungemia, and exhibit a very high mortality rate[8,18].

While comprehensive studies detailing the specific pathogenesis of *K. ohmeri* infections are currently lacking, the resemblance between endogenous infection of *K. ohmeri* and *Candida* spp. prompts the authors to hypothesize a shared pathophysiology. Recent reviews suggest that many risks associated with invasive candidiasis are iatrogenic in nature[15]. Factors such as gut dysbiosis induced by broad-spectrum antibiotics, leading to heightened yeast colonization and invasion in the intestines, have been identified[19]. Furthermore, the disruption of cutaneous and intestinal barriers resulting in bloodstream translocation can occur due to central venous catheters, chemotherapy-induced mucositis, and surgical interventions[16]. Conditions like neutropenia, immunosuppression, or corticosteroid use can compromise protective phagocyte-dependent antifungal responses[15].

When considering the recommended antifungal therapy for *K. ohmeri* infection, the absence of standardized methods for antifungal susceptibility testing and established clinical breakpoints makes it challenging to determine which antifungal agent would be more effective than others. However, a recent review reveals consistently higher MIC for fluconazole compared to amphotericin B and echinocandins. In line with this research, *K. ohmeri* exhibited a fluconazole MIC50 of 8 µg/dL. This indicates that over half of the isolates could be classified as resistant to fluconazole when clinical breakpoints for *Candida* spp. are taken into account[8,20]. Consequently, the authors suggest initiating empirical treatment using either amphotericin B or echinocandins, optionally combined with fluconazole. A subsequent shift to fluconazole monotherapy is recommended once stable clinical signs emerge and the pathogen's MIC can be attained with a non-toxic dosage of the drug. If the MIC of the pathogen is moderately high compared to clinical breakpoints of *Candida* spp., a high dose of fluconazole, for example, 12 mg/kg/day, is recommended. Alternatively, other new generation azoles such as itraconazole or voriconazole can be considered, depending on the MIC. Several case reports have indicated successful treatment outcomes from such regimens[5,6].

Notably, a discernible contrast was observed. In the first case, a male patient with fewer predisposing factors received intravenous fluconazole exclusively for 14 days, resulting in a successful and expedited resolution of fungemia. Intriguingly, repeated hemocultures conducted prior to the initiation of fluconazole treatment yielded negative results, suggesting a potential spontaneous resolution of *K. ohmeri* infection in immunocompetent individuals. A prior case report documented a psychotic patient experiencing transient *Saccharomyces cerevisae* fungemia after self-injection without antifungal intervention[21]. However, as only about half of fungemia cases can be detected using bacterial culture techniques[22], we are unable to address the lack of benefit from high-dose fluconazole in such instances. On the other hand, in the second case, a boy with cyclic neutropenia and buttock gangrene later developed CRBSI due to *K. ohmeri*. Despite receiving appropriate combined antifungal agents, he experienced a persistent 78-day interval of fungemia. Additionally, he displayed thrombosis of the internal jugular vein at the site where the infected catheter used to be inserted. This finding reflects that the rate of fungal clearance depends on the ability of source control and host immunity[7].

Finally, we do not believe that these three cases share an epidemiological connection and can be classified as an outbreak. While the first and second cases occur within the same timeframe, they are admitted to different wards and are under entirely different healthcare teams. The third case occurs approximately nine months later. However, the limitation of this hypothesis lies in the absence of an investigation.

In conclusion, *K. ohmeri* infection remains infrequent, yet its associated high mortality rate and limited treatment options underscore the critical need for extensive systematic reviews. The existing knowledge emphasizes a proactive approach to prevention, involving efforts to mitigate risks through initiatives such as antibiotic stewardship and the management of underlying conditions, especially the immunologic status of the patient who is at risk.

Ethics approval

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE661595).

Funding statement

None

Acknowledgements

The authors thank the Department of Medicine, Faculty of Medicine, Khon Kaen University for publication support.

What is already known on this topic?

K. ohmeri is an emerging pathogenic fungus in humans, especially among immunocompromised patients. It is associated with a high mortality rate and typically exhibits elevated MICs to fluconazole.

What this study adds?

The pathogenesis of *K. ohmeri* infection can be classified based on the route of infection, distinguishing between exogenous and endogenous routes. Patients with endogenous *K. ohmeri* infection share similar risk factors with those experiencing invasive candidiasis. In Thailand, MICs of *K. ohmeri* to fluconazole are consistently high, mirroring findings in previous case reports from other countries. Empirical treatment choices, especially in seriously ill patients awaiting susceptibility test results, often involve amphotericin B or echinocandins.

Conflicts of interest

The authors have no conflict of interests.

References

1. Yamada Y, Suzuki T, Matsuda M, Mikata K. The phylogeny of *Yamadazyma ohmeri* (Etchells et Bell) Billon-Grand based on the partial sequences of 18S and 26S ribosomal RNAs: the proposal of *Kodamaea* gen. nov. (Saccharomycetaceae). Biosci Biotechnol Biochem 1995;59:1172-4.
2. Sharma S, Arora A, Sharma P, Singh S, Nain L, Paul D. Notable mixed substrate fermentation by native *Kodamaea ohmeri* strains isolated from *Lagenaria siceraria* flowers and ethanol production on paddy straw hydrolysates. Chem Cent J 2018;12:8.
3. Mahfouz RA, Otrock ZK, Mehawej H, Farhat F. *Kodamaea (Pichia) ohmeri* fungaemia complicating acute myeloid leukaemia in a patient with haemochromatosis. Pathology 2008;40:99-101.
4. João I, Duarte J, Cotrim C, Rodrigues A, Martins C, Fazendas P, et al. Native valve endocarditis due to *Pichia ohmeri*. Heart Vessels 2002;16:260-3.
5. Yang BH, Peng MY, Hou SJ, Sun JR, Lee SY, Lu JJ. Fluconazole-resistant *Kodamaea ohmeri* fungemia associated with cellulitis: case report and review of the literature. Int J Infect Dis 2009;13:e493-7.
6. Diallo K, Lefevre B, Cadelis G, Gallois JC, Gandon F, Nicolas M, et al. A case report of fungemia due to Kodamaea ohmeri. BMC Infect Dis 2019;19:570.
7. Rosli T, Radhakrishnan AP, Thabit AAM, Sukur SM. A case report: persistent *Kodamaea ohmeri* fungaemia due to peritoneal infection. Open Access Libr J 2023;10:e9730.
8. Zhou M, Li Y, Kudinha T, Xu Y, Liu Z. *Kodamaea ohmeri* as an Emerging Human Pathogen: A Review and Update. Front Microbiol 2021;12:736582.
9. Germeshausen M, Deerberg S, Peter Y, Reimer C, Kratz CP, Ballmaier M. The spectrum of ELANE mutations and their implications in severe congenital and cyclic neutropenia. Hum Mutat 2013;34:905-14.
10. The European Committee on Antimicrobial Susceptibility Testing. Overview of antifungal ECOFFs and clinical breakpoints for yeasts, moulds and dermatophytes using the EUCAST e.Def 7.3, e.Def 9.4 and e.Def 11.0 procedures [Internet]. Version 3. 2022 [cited 2023 Jan 13]. Available from: https://www.eucast.org/astoffungi/clinicalbreakpointsforantifungals.
11. Weerasekera MM, Sissons CH, Wong L, Anderson S, Holmes AR, Cannon RD. Use of denaturing gradient gel electrophoresis for the identification of mixed oral yeasts in human saliva. J Med Microbiol 2013;62:319-30.
12. Gonçalves RH, Miranda ET, Zaia JE, Giannini MJ. Species diversity of yeast in oral colonization of insulin-treated diabetes mellitus patients. Mycopathologia 2006;162:83-9.
13. Li ZM, Kuang YK, Zheng YF, Xu PH, Wang JY, Gan RJ, et al. Gut-derived fungemia due to *Kodamaea ohmeri* combined with invasive pulmonary aspergillosis: a case report. BMC Infect Dis 2022;22:903.
14. Sayed Hitam SA. A case report of *Kodamaea ohmeri* infection. Int J Infect Dis 2020;101:386.
15. Lionakis MS, Drummond RA, Hohl TM. Immune responses to human fungal pathogens and therapeutic prospects. Nat Rev Immunol 2023;23:433-52.
16. Shaaban H, Choo HF, Boghossian J, Perez G. *Kodamaea ohmeri* fungemia in an immunocompetent patient treated with micafungin: case report and review of the literature. Mycopathologia 2010;170:223-8.
17. Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: Current epidemiological trends. Clin Infect Dis 2006;43 Suppl 1:S3-14.
18. Son BR, Shin KS. *Kodamaea ohmeri* fungemia in a patient with carcinoma of the ampulla of Vater. J Biomed Transl Res 2016;17:36-9.
19. Fan D, Coughlin LA, Neubauer MM, Kim J, Kim MS, Zhan X, et al. Activation of HIF-1α and LL-37 by commensal bacteria inhibits *Candida albicans* colonization. Nat Med 2015;21:808-14.
20. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antifungal susceptibility testing of yeasts. 3rd ed. CLSI supplement M27M44S. Wayne, PA: CLSI; 2022.
21. Cohen L, Ranque S, Raoult D. *Saccharomyces cerevisiae boulardii* transient fungemia after intravenous self-inoculation. Med Mycol Case Rep 2013;2:63-4.
22. Zheng S, Ng TY, Li H, Tan AL, Tan TT, Tan BH. A dedicated fungal culture medium is useful in the diagnosis of fungemia: a retrospective cross-sectional study. PLoS One 2016;11:e0164668.