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Original Article

The Emerging Life-threatening Opportunistic Fungal Pathogen *Kodamaea ohmeri*: Optimal Treatment and Literature Review

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BACKGROUND/PURPOSE: The yeast *Kodamaea ohmeri* rarely causes life-threatening human infections. However, risk factors, laboratory diagnoses, and treatments for *K. ohmeri* infection have been limited, and the optimal therapy for *K. ohmeri* infection has not been identified.

METHODS: Twenty cases of *K. ohmeri* infection have been reported in the English medical literature. We present two new cases of *K. ohmeri* fungemia. We investigated the nature and treatment of *K. ohmeri* infections using minimum inhibitory concentrations of antifungal agents and by comparing the two cases with those described in the literature.

RESULTS: From March 1998 to December 2008, a total of 22 patients with *K. ohmeri* infections were studied. Hematological malignancies and diabetes were the most common co-morbidities for *K. ohmeri* infections, with crude prevalence rates of 27.3% and 18.2%, respectively. The *K. ohmeri* isolates showed less susceptibility to fluconazole but greater susceptibility to amphotericin B [15/25 isolates (60%) *vs.* 25/25 isolates (100%), respectively]. Good outcomes (8/9 cases; 88.9%) were found following removal of indwelling catheters and implants. In addition, voriconazole and echinocandins, such as caspofungin and micafungin, also showed excellent minimum inhibitory concentrations against *K. ohmeri*.

CONCLUSION: *K. ohmeri* should not be regarded as a contaminant of blood cultures. Favorable outcomes for this potentially life-threatening infection are promoted by the removal of indwelling catheters; furthermore, outcomes are associated with optimal antifungal regimens, especially voriconazole and echinocandins.

KEYWORDS: echinocandins, fluconazole, fungemia, *Kodamaea ohmeri*, voriconazole

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Introduction

Fungi are being increasingly recognized as major pathogens in critically ill patients. *Candida* spp., *Aspergillus* spp., and *Cryptococcus* spp. comprise the majority of isolates in invasive fungal infections.[1,2] Other yeasts and filamentous fungi, such as *Blastomyces dermatitidis*, dematiaceous fungi, *Coccidioides* spp., *Fusarium* spp., *Histoplasma capsulatum*, *Scedosporium* spp., *Trichosporon* spp., *Penicillium* spp., and Zygomycetes are emerging as significant human pathogens.[2,3] Over the past decades, *Kodamaea ohmeri* has been recognized as an opportunistic pathogen, especially in immunocompromised patients.[4] This fungus has been rarely reported in the medical literature published since 1970. This report presents two new patients with a *K. ohmeri* infection that occurred within the same hospital service, and a review of previously reported cases.

Methods

We conducted a search (using the MEDLINE database) of the English medical literature from January 1970 to December 2008 using the following keywords: *Pichia*, *Kodamaea ohmeri,* and yeast. We found 20 reported cases of *K. ohmeri* infection.[4–16] Here, we report two new cases of *K. ohmeri* fungemia, one with concomitant cellulitis.

Case 1

A 71-year-old man was admitted to our hospital with fever, disturbance of consciousness, and cellulitis in his right leg. He had type 2 diabetes, coronary artery disease, iatrogenic Cushing's syndrome, major depression, and post-surgical herniation of an intervertebral disc in the lumbar spine. On admission, his body temperature was 39.3°C, heart rate was 84 beats/min; respiratory rate was 24 breaths/min, and blood pressure was 130/80 mmHg. Physical examination revealed erythema and swelling of his right leg. A complete blood cell count showed a white cell count of 7×10^9/L with 74.9% neutrophils, and a C-reactive protein level of 78 mg/L. Blood biochemistry showed glucose was 14.4 mmol/L, triglycerides 8.1 mmol/L, and uric acid 487.7 umol/L. All other parameters were normal. The findings of urine analysis, chest radiograph, and an electrocardiogram were normal. The patient was empirically administered intravenous oxacillin for the treatment of his cellulitis. A yeast-like organism was isolated from the patient's blood, and he was given intravenous fluconazole (400 mg/day). Transthoracic echocardiography showed no evidence of vegetation of the cardiac valves. The yeast was identified as *K. ohmeri*. The patient remained febrile despite fluconazole therapy; therefore, the antifungal regimen was changed to amphotericin B deoxycholate (0.5 mg/kg/day). Two weeks after this new treatment, the cellulitis in his right leg improved and subsequent blood cultures were negative.

Case 2

A 58-year-old woman was admitted to our hospital with dysphagia and a weight loss of 10 kg in the previous 3 weeks. She had a history of esophageal squamous cell carcinoma with multiple metastases, including brain, lung, and liver. On admission, her body temperature was 37°C, heart rate was 84 beats/min, respiratory rate was 19 breaths/min, and blood pressure was 120/90 mmHg. Her blood white cell count was 10.2×10^9/L with 74.0% neutrophils. On the 3rd day of hospitalization, she was given a percutaneous endoscopic gastrectomy and underwent placement of a peripherally inserted central catheter into the left basilic vein. On the 17th day of hospitalization, the patient was given intravenous imipenem-cilastatin to treat pneumonia in her left lung. Her fever resolved after therapy, but it recurred on the 28th day of hospitalization. A yeast-like organism was isolated from her blood, and intravenous fluconazole (400 mg/day) was started. The yeast was identified as *K. ohmeri* and was susceptible to fluconazole. The same yeast was isolated from her blood on the 38th day of hospitalization. The patient died on the 45th day of hospitalization. However, the last blood culture, performed 1 day before the patient died, showed no growth of *K. ohmeri*.

Mycological studies

Blood cultures from the two cases were performed using the BacT/ALERT Microbial Detection System (bioMèrieux SA, Marcy-l'Etoile, France). The isolates from the cases were identified in our laboratory via morphological (Sabouraud-Dextrose agar, Corn Meal agar, and CHROMagar) and biochemical methods (Vitek 2 YST, bioMèrieux, Hazelwood, Mo, USA). The susceptibility to antifungal agents was tested

using the ATB Fungus 3 system (bioMèrieux SA, Marcy-l'Etoile, France) according to the manufacturer's instructions.

In 2007, the Clinical and Laboratory Standards Institute [CLSI; formerly the National Committee for Clinical Laboratory Standards (NCCLS)] published an approved reference method for broth microdilution testing (CLSI document M27-A3) of yeasts.[17] This method was developed through a consensus process to facilitate agreement among laboratories in determining the susceptibility of yeasts to several antifungal agents. The acceptable percent essential agreement for minimum inhibitory concentrations (MICs) was set at ≥90% for each antifungal agent against all organisms tested. Reference MICs were determined after 48 hours of incubation. The breakpoints in the antifungal susceptibility testing of yeasts, as defined by the CLSI, showed MICs of ≤1, ≤8, ≤0.125, ≤1, ≤2, ≤2 and ≤4 mg/L, to amphotericin B, fluconazole, itraconazole, voriconazole, caspofungin, micafungin, and flucytosine, respectively.[17]

Results

From March 1998 to December 2008, a total of 22 patients with *K. ohmeri* infections, including the present cases, were enrolled in this study. The yeast morphotype in the present cases showed white-rough colonies on Sabouraud-Dextrose agar plates, and underwent a change from pink to blue on CHROMagar plates (Figure). The demographic data and clinical characteristics of patients with *K. ohmeri* infection are listed in Table 1.

Sixteen males and six females (i.e. male-to-female ratio of ~3:1) were enrolled. The ages ranged from a newborn baby to 84 years, with the mean age being 42 years. Infections included fungemia (19 cases, with 1 cellulitis, 1 phlebitis, 2 endocarditis, and 4 catheter infection cases; and 3 cases involving children), polymicrobial wound infection (1 case), urinary tract infection (1 case) and peritonitis (1 case). Hematological malignancy and diabetes were the two most common co-morbidities (27.3% and 18.2%, respectively). Other reported predisposing factors included neutropenia (4 cases), malignant solid tumors (3 cases), infant (3 cases), renal failure (2 cases), organ transplantation (1 case), hemochromatosis (1 case), and intravenous drug use (1 case). The presence of indwelling catheters or implants was an important risk factor associated with *K. ohmeri* infection, and removal of these catheters and implants was critical for successful management (8/9 cases; 88.9%).

The MICs of the antifungal agents used to treat the *K. ohmeri* strains isolated from the enrolled cases are shown in Table 2. Of the drugs tested, 60% of the isolates (15/25) showed MICs of ≤8 mg/L for fluconazole, and 100% of the isolates (25/25) demonstrated MICs of ≤1 mg/L for amphotericin B; these are the reference breakpoints. Most cases treated with fluconazole therapy had poor responses or outcomes (12/15 cases; 80%). In addition, more than three-quarters (10/13 cases; 76.9%) of the patients who received amphotericin B-based therapy (either alone, or associated with flucytosine, or fluconazole) had favorable outcomes. Furthermore, the extended-spectrum antifungal agents, triazole and echinocandins, were found to have

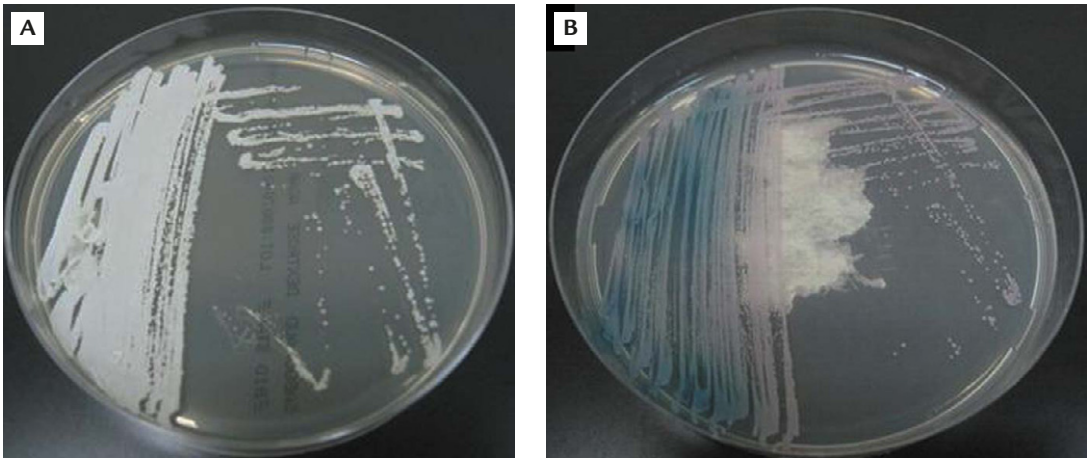

Figure. Appearance of *Kodamaea ohmeri* on (A) Sabouraud-Dextrose agar and (B) CHROMagar plates.

Table 1. Clinical characteristics of *Kodamaea ohmeri* infection in English medical literatures and the present cases

Case	Age (yr)	Sex	Underlying condition(s)/ risk factor(s)	Source of culture	Catheter status/ prosthetic implants	Drug therapy	Outcome	Reference
1	48	F	Diabetes, kidney transplant	Blood	CVC, not removed	Flu, AmB	Expired	4
2[a]	38	F	AML, hemochromatosis, neutropenia	Blood, catheter	Peripheral catheter, removed	Flu, AmB	Recovered	5
3	59	M	VP shunt infection, nosocomial pneumonia	Blood, phlebitis	Peripheral catheter, removed	AmB	Recovered	6
4	11	M	Burkitt's lymphoma, neutropenia	Blood	CVC	Flu	Expired	6
5	41	M	Alcoholic ketoacidosis, tuberculosis	Blood	CVC	–	Recovered	6
6	47	M	Pneumonia, diabetes, chronic renal failure	Blood	CVC	AmB, Flu	Expired	6
7	4	F	Tetralogy of Fallot	Blood	CVC	AmB, Flu	Expired	6
8	0	F	Infant and vein catheter	Blood	Umbilical artery	–	Recovered	6
9	58	F	CML catheter tip	Blood,	HDLC, removed	AmB	Recovered	7
10	0	F	Infant	Blood	–	AmB, Flu	Recovered	8
11	0	M	Encephalitis	Blood	–	Flu	Expired	9
12	10	M	ALL, neutropenia	Blood	CVC	AmB	Recovered	9
13	14	M	ALL, neutropenia catheter tip	Blood,	PAC, removed	Flu	Recovered	10
14	75	M	Fibrous histiocytoma with wound	Wound	–	Flu	Expired	10
15	42	M	MV endocarditis, IVDU, hepatitis C	Blood, vegetation	VR	FC, AmB	Recovered	11
16	73	M	Hodgkin lymphoma	Urine	Urinary catheter	Flu	Recovered	12
17	84	M	SCC of sinus catheter tip	Blood,	CVC, removed	Flu, AmB	Recovered	13
18	76	M	Prosthetic MV endocarditis, pacemaker	Blood, vegetation	VR; pacemaker removed	Flu, AmB	Recovered	14
19	71	M	TV endocarditis, pacemaker, diabetes	Blood, catheter tip	CVC, removed	AmB	Expired	15
20	64	M	Peritoneal dialysis fluid	Peritoneal removed	Tenckhoff catheter,	Flu, AmB	Recovered	16
21	71	M	Cellulitis, diabetes, iatrogenic Cushing syndrome	Blood removed	Peripheral catheter,	Flu, AmB case	Recovered	Present
22	48	M	SCC of esophagus, nosocomial pneumonia	Blood	PICC	Flu case	Expired	Present

[a]Case 2 is reported by Shin DH et al, 2003 [6]. ALL=Acute lymphoblastic leukemia; AmB=amphotericin B; AML=acute myeloid leukemia; CML=chronic myelogenous leukemia; CVC=central venous catheter; FC=flucytosine; Flu=fluconazole; HDLC=Hickmann double-lumen catheter; IVDU=intravenous drug user; MV=mitral valve; PAC=Port-a catheter; PICC=peripherally inserted central catheter; SCC=squamous cell carcinoma; TV=tricuspid valve; VP shunt=ventriculoperitoneal shunt; VR=valve replacement.

Table 2. Antifungal susceptibility testing results for *Kodamaea ohmeri* isolates from cases in English medical literatures and the present study

Case	Isolate no.	Source	AmB	Flu	Itra	Vori	Casp	Mica	FC	Reference
1	1-1	Blood	–	–	–	–	–	–	–	4
2[a]	2-1	Blood	–	–	–	–	–	–	–	5
	2-2	Catheter	–	–	–	–	–	–	–	
3	3-1	Blood	0.50	4	0.125	0.06	0.25	0.06	–	6
	3-2	Blood	0.50	4	0.125	0.06	0.25	0.06	–	
	3-3	Phlebitis site	0.50	4	0.125	0.06	0.125	0.06	–	
4	4-1	Blood	0.25	32	0.50	0.50	0.125	0.03	–	6
	4-2	Catheter	0.25	32	0.50	0.50	0.125	0.03	–	
	4-3	Blood	0.50	32	0.50	0.50	0.125	0.03	–	
5	5-1	Blood	0.25	16	0.25	0.125	0.25	0.06	–	6
	5-2	Blood	0.25	16	0.25	0.125	0.25	0.06	–	
6	6-1	Blood	0.25	4	0.125	0.125	0.125	0.03	–	6
	6-2	Catheter	0.25	4	0.125	0.03	0.125	0.03	–	
	6-3	Blood	0.50	4	0.125	0.03	0.125	0.03	–	
7	7-1	Blood	0.25	16	0.125	0.06	0.125	0.03	–	6
8	8-1	Blood	0.50	2	0.125	0.03	0.125	0.03	–	6
9	9-1	Blood	0.50	4	–	–	–	–	–	7
	9-2	Catheter	–	–	–	–	–	–	–	
10	10-1	Blood	0.064	32	0.25	–	–	–	<0.002	8
	10-2	Blood	–	–	–	–	–	–	–	
11	11-1	Blood	0.008	8	–	–	–	–	–	9
12	12-1	Blood	0.008	8	–	–	–	–	–	9
13	13-1	Blood	0.50	32	0.25	–	–	–	–	10
14	14-1	Wound	1.00	32	0.008	–	–	–	–	10
15	15-1	Vegetation	–	–	–	–	–	–	–	11
16	16-1	Urine	Sus	Sus	Sus	–	–	–	Sus	12
17	17-1	Blood	–	–	–	–	–	–	–	13
	17-2	Catheter	–	–	–	–	–	–	–	
18	18-1	Vegetation	0.25	4	0.03	–	–	–	≤0.125	14
19	19-1	Blood	–	–	–	–	–	–	–	15
20	20-1	Peritoneal fluid	–	–	–	–	–	–	–	16
21	21-1	Blood	0.50	64	0.50	–	–	–	<0.50	Present case
22	22-1	Blood	0.50	8	0.125	0.125	–	–	<4	Present case
	22-2	Blood	0.50	8	0.125	0.125	–	–	<4	
	22-3	Blood	0.50	8	0.125	0.125	–	–	<4	

[a]Patient 2 is reported by Shin DH et al, 2003 [6]. AmB=Amphotericin B; Casp=caspofungin; FC=flucytosine; Flu=fluconazole; Itra=itraconazole; Mica=micafungin; Sus=reported as "susceptibility" only; Vori=voriconazole.

MICs of ≤0.50 (16/16; 100%), ≤0.25 (13/13; 100%), and ≤0.06 (13/13; 100%) mg/L to voriconazole, caspofungin, and micafungin, respectively. These are excellent MICs in comparison to the reference standards.

Discussion

The epidemiology of yeast infections has undergone significant changes over the last several decades,[2] and the annual incidence of fungemia has increased since the 1980s. The yeast *K. ohmeri*, previously known as *Pichia ohmeri* or *Yamadazyma ohmeri*, belongs to the *Saccharomycetaceae* family.[18] The first documented case was in an immunocompromised patient with *K. ohmeri* fungemia, reported in March 1998.[4] It was first classified as *Endomycopsis ohmeri*[19] and later transferred to the genus *Pichia* by Hansen.[20] *K. ohmeri* has been placed in the guilliermondii-fibuligera group.[21]

The epidemiology of invasive fungal infections in humans has changed significantly in the past decade. This is probably due to the use of broad-spectrum antibiotic therapy and antifungal prophylaxis, especially in hematologic patients.[1] *K. ohmeri* is an emerging opportunistic pathogen in clinical practice, and it should not be regarded as a contaminant of blood cultures. Although the most common risk factors for fungal infection have mainly been described in immunocompromised patients,[3] there is limited data on the risk factors, laboratory analysis, treatment, and prevention of *K. ohmeri* infection. From our review, *K. ohmeri* infections mainly occur in immunocompromised patients,[4–10,12–13,15,16] and less frequently in immunocompetent patients.[6,11] In addition, indwelling catheters and implants are important risk factors associated with *K. ohmeri* infections.[4–7,9,10,12–16]

Most yeasts are identified on the basis of carbohydrate assimilation and/or fermentation, and their macroscopic and microscopic morphological features after growth on specialized media. Two assays for yeast identification are the commercially available Vitek and API 20C assays. Although the API 20C assay is considered to be the gold standard for identification of *K. ohmeri* and other yeast species, a high false-positive rate with regard to *K. ohmeri* has been reported.[6] CHROMagar *Candida* chromogenic growth medium is an extremely useful tool for the identification of *K. ohmeri* and *Candida* species. This assay is based on the growth of colored colonies.[6] On a CHROMagar plate, *K. ohmeri* colonies undergo a characteristic change from pink to blue.[6,9,12] This unique characteristic is a simple and useful tool for the detection of *K. ohmeri*.

Because of the poor prognosis for patients with invasive fungal infections, optimal treatments and/or antifungal strategies are important. Antifungal treatments include fluconazole, amphotericin B, or flucytosine, and these treatments can be combined with catheter removal, valve replacement, and surgical debridement (Table 1). Various antifungal regimens have been used to treat *K. ohmeri* infections, but fluconazole therapy has often been associated with poor responses and poor outcomes.[4–6,9,10,13,14,16] While the optimal treatment for *K. ohmeri* infections are yet to be determined, our review shows good outcomes after removal of the indwelling catheters, pacemakers, and vegetated cardiac valves.[5–7,10,13,14,16] Furthermore, *K. ohmeri* seems to be resistant to fluconazole but is susceptible to amphotericin B.[22] In addition to these antifungal agents, the expanded-spectrum antimicrobials triazole, voriconazole, and the echinocandins, caspofungin and micafungin, have shown excellent MICs against *K. ohmeri* in previous reports and in our patients (Table 2); however, clinical experience with these agents in this setting is lacking.

In conclusion, *K. ohmeri* can cause life-threatening infections. Favorable outcomes for this potentially life-threatening fungal infection are likely to be associated with early diagnosis, optimal antifungal regimens, and the removal of indwelling catheters. It should be pointed out that fluconazole is the least effective against *K. ohmeri* infections. Although further study is needed to establish the optimal antifungal regimens, voriconazole and echinocandins are suggested in treating *K. ohmeri* infections.

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