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Kodamaea ohmeri, An Emerging Yeast in Tunisia: First Identification in Three Case Reports and Literature Review

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Abstract

Background: *Kodamaea ohmeri* or *Pichia ohmeri* is relatively rare yeast that belongs to ascomycete group and Saccharomycetaceae family. It is recognized as an important pathogenic fungus in immunocompromised hosts.

Methodology: Herein, we describe three cases where *Kodamaea ohmeri* was isolated in peripheral samples: nasal in one case and auricular in two cases. The identification was carried out by Vitek®2 YST ID card and confirmed by PCR sequencing. Susceptibility to antifungal was made by E-test.

Results: These yeasts were identified *K. ohmeri* using phenotypic, biochemical and molecular methods. All isolates were susceptible for voriconazole and amphotericin B, resistant for caspofungin and susceptible-dose-dependent for Fluconazole.
Conclusion: These are firsts cases reported in Tunisia which incites to pay more attention to the emergence of this yeast in human pathology since more it develops resistances to antifungals.

Keywords: *Kodamaea ohmeri*; Identification; Otitis; Echinocandin

Introduction

Kodamaea ohmeri, previously known as *Pichia ohmeri* or *Yamadazyma ohmeri*, is relatively rare yeast that belongs to ascomycete group and Saccharomycetaceae family [1,2]. It is the teleomorphic form of *Candida guilliermondii* var. *membranaefaciens* and is widely used in the food industry for the fermentation of fruits, pickles and rinds [3]. Now, genus Kodamaea is divided into 5 species and only *K. ohmeri* shows pathogenicity in humans [1]. This fungus is frequently misidentified as a *Candida* species [2]. Recently, *K. ohmeri* was recognized as an important pathogenic fungus in immunocompromised hosts [1]. Herein, we describe three cases where *Kodamaea ohmeri* was isolated in peripheral samples. The identification was carried out by Vitek®2 YST card and PCR sequencing. Susceptibility to antifungal was tested by E-test.

Materials and Methods

Case description

Case 1: A 61-year-old man diabetic, coronary, having nasal hyperreactivity syndrome consults for hearing loss, left ear buzzing for 15 days. At examination, he had purulent otorrhea, inflammatory mucosa and congestive eardrum. The auricular sample isolates *Staphylococcus aureus* Methicillin sensitive. He was treated with Ciprofloxacin and Augmentin for 10 days without improvement. A second auricular sample isolates *Candida krusei, Aspergillus niger and Kodamaea ohmeri*. He was treated by washing of auditory external canal with hydrogen peroxide, betadine and auricularum ear drops. He was checked after 3 months with a good evolution.

Case 2: A 55-year-old man hypertensive, stented, diabetic and depressive, consults for earaches since 5 days with fullness sensation of the right ear. On examination, auditory external canal was congestive and stenosis at 50%. White deposits have been seen. The mycological sample isolates *Candida albicans* and *Kodamaea ohmeri*. He was treated by washing of auditory canal with hydrogen peroxide and by auricularum drops with a good evolution.

Case 3: A 68-year-old man admitted to the intensive care unit for abdominal pain, anorexia and impaired consciousness. His history included hypertension, dyslipidemia, gastrointestinal bleeding, stroke and total left hip prosthesis. His explorations: brain scan: osteolytic lesion of the base of the left cranium of 15 mm with fuzzy limits invading the left cavernous lodge and the meningeal spaces. PET scan: Hypermetabolic lesion of pancreas with axial and peripheral osteomedullary diffuse hypermetabolic lesions, secondary hepatic lesions of segments 2 and 3, and celiaclymphadenopathy. At the admission, his Glasgow score was 11/15. He was apyretic and had diffuse abdominal tenderness. Body scan showed pancreas swollen in its caudal portion seat of a hypodense lesion measuring 10 mm of long, with infiltration of mesenteric fat, lomboaortic and coeliomenteric lymphadenopathies, hepatic secondary lesions of segments 4, 6, 7 and 8, left pleural effusion with ventilator disorder of pulmonary bases.

Biological explorations revealed hemoglobin 6.5 g/dl, urea 12.8 mmol/l, creatine 99 µmol/l, ASAT/ALAT 160/140 U/ml, lipase 76 U/ml, CPK 643 U/ml, LDH 630 U/ml, CRP 118 mg/l, procalcitonin 3.61 ng/ml, bacteriological and mycological blood cultures were negative.

Among cutaneous-mucosal control samples: buccal sampling isolated

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Candida glabrata and *Candida dubliniensis*; nasal sample isolates: *Kodamaea ohmeri*.

The patient was treated with Augmentin as a probabilistic antibiotic for pulmonary infection and palliative treatment with opioid morphines with initially good resolution and then had non recoverable cardiopulmonary arrest and died.

Methods

For each sample, direct examination and culture on Sabouraud Chlaramphenicol (SC) medium, SC supplemented with Actidione and CHROMagar medium (Beckton Dickinson, Paris, France) were carried out. The identification was based on the results of chlamydosporulation test on Tween agar medium, Vitek®2 compact (YST bioMérieux, France) and PCR sequencing of the internally transcribed spacer (ITS). The primers used were Its1 (5'-TCCGTAGGTGAACCTGCGG-3') and Its4 (5'-TCCTCCGCTTATTGATATGC-3') as described by Koebel et al. [4].

The antifungal susceptibility of the three isolates was determined in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) by using RPMI 1640 medium and E test [5].

Results

Direct examination showed yeasts for all samples. After 48 h of subculture at 37°C on SC medium, strains of *K. ohmeri* grew forming white creamy colonies (Figure 1). On CHROMagar (Beckton Dickinson, Paris, France), the yeasts exhibited membranous colonies that changed color from pink to blue within 48 hours only for isolate N°3 (Figure 2). On Tween agar, all strains showed pseudohyphae and blastoconidia 24 hours later at 27°C (Figure 3). The phenotypically identity of the 3 isolates was also determined by Vitek®2 YST card with 99.9% probability. The molecular identification showed that sequences matched in 99% with previous *K. ohmeri* in GeneBank.

All isolates were susceptible for voriconazole and amphotericin B, resistant for caspofungin and susceptible-dose-dependent for fluconazole. Results of identification tests and antifungal susceptibility are listed in Table 1.

Discussion

Kodamae ohmeri had been recognized as a fungal contaminant but not as pathogen. The first clinical isolate was reported in 1984 from a pleural fluid sample. At the same year, the first case of sepsis due to *K. ohmeri* was reported [1]. Since then, more infections with this yeast have been reported considering it as an important pathogen fungus, especially in patients with underlying immunosuppression [1,6,7].

Table 2 summarize the literature data on 20 case reports of *K. ohmeri* infections. Most case reports were from Asia (12/20, 60%), whereas the others were from Europe (3/20, 15%), America (3/20, 15%) and the Middle East (1/20, 5%). It has been described in various studies that most of cases were from Asia [2,7-10]. In four cases (20%), this infection concerned new-borns of whom two were premature. Kanno et al. reported that most cases occur in children than in adults and among them 39% were reported in paediatric age group [2]. Finally, most of the cases has been reported in patients presenting severe pathological immunosuppression associated with hematologic or solid neoplasms use of immunosuppressive drug, type 2 diabetes mellitus and HIV seropositive [2,6,7,9,11-16]. Significant correlation with *K. ohmeri* infections has been demonstrated for the use of invasive procedures and antibiotic agents [1-4,6,8-10,12-15]. Among our three cases, two were diabetics and one having metastatic pancreatic cancer. Two cases were treated with antibiotics before fungal infection.

K. ohmeri has been identified as a cause of fungemia essentially (16/20, 80%), endocarditis (3/20, 15%) and funguria (3/20, 15%). Whereas it was also isolated from respiratory samples, peritoneal fluid, catheter, wound lesion and oral lesion [1,2,4,10,13,16]. It is described even in vaginal sample [6]. Our third case is the first in literature describing *K. ohmeri* in nasal sample. Whereas the two other cases were the seconds reporting otitis infections with this yeast. In fact, Son et al. reported the first case of malignant external otitis [9].

The CHROMagar Candida medium allows an easy species isolation and identification according to the colour changes of the colonies which was observed in one of our strains [10,17-19]. The two others isolate had not changed their colour as was reported by Otag et al. [20].

At present, biochemical identification was successfully done by Vitek®2 YST. It identifies this yeast with accuracy, although there have been some false results identifying *K. ohmeri* as C. haemulonii [19]. Similarly, the use of the API 20C test may lead to false results, by which some species of C. haemulonii or C. parapsilosis are misidentified as *K. ohmeri* [1,19].

Some studies reported the identification of *K. ohmeri* using MALDI-TOF mass spectrometer and then confirmed the strains by molecular methods [7,21]. However, they obtained an irrelevant score using this technique: 85.2% of fiability according to the study of Distasi et al. [7] and a score of 1.548 according to the study of Chenrui et al.

Thus, molecular identification is mandatory. In the cases reported here, molecular diagnosis is available through the amplification and sequencing of the ITS2 region. Previous studies reported that sequence analysis of the D1/D2 domains of the 26S rRNA gene and of genomic DNA through restriction endonucleases by pulsed field gel electrophoresis are also useful [9].

Isolate N°	Case N°	Source	Vitek® 2 ID-YST (result)[a]	Color change (pink to blue) of colonies on CHROMagar	Identification by Its2 sequencing (%) [b]	FLU	VCZ	CAS	AMB
						MIC (µg/ml) (DS)			
1	1	auricular	*K. ohmeri* (excellent)	No	*K. ohmeri (99%)*	4 (SDD)	0.032 (S)	>32 (R)	0.094 (S)
2	2	auricular	*K. ohmeri* (excellent)	No	*K. ohmeri (99%)*	4 (SDD)	0.032 (S)	>32 (R)	0.125 (S)
3	3	Nasal	*K. ohmeri* (excellent)	**Yes**	*K. ohmeri (99%)*	3 (SDD)	0.032 (S)	>32 (R)	0.094 (S)

*The probability of correct identification is indicated in parentheses.
*Numbers in parentheses are percentages of homology of the ITS2 sequences of the isolates to the reference sequence of *K. ohmeri*.
AMB: Amphotericin B; FLU: Fluconazole; VCZ: Voriconazole; CAS: Caspofungin
DS: Drug sensitivity; S: Susceptible, R: Resistant, SDD: Susceptible dose dependent according to CLSI breakpoints

Table 1: Results of identification tests and antifungal susceptibility for *K. ohmeri* strains.

Age/Gender	Background	Source	Antifungal	Outcome	Country	References
25/M	alcoholic, cranial trauma	catheter related bloodstream infection	Caspofungin	Survived	China	[22]
60/F	Severe burn, autograft	Fungemia, wound lesion	Micafungin (low S) → liposomal AMB	Died	Japan	[1]
58/F	Rheumatoid arthritis, breast cancer	Fungemia, catheter	Micafungin	Survived	Japan	[2]
57/M	Hemophagocytic lymphohistiocytosis	Fungemia, endocarditis	Voriconazole	Survived	China	[3]
Infant (54 days)/ M	Premature	Fungemia	Caspofungin	Survived	Colombia	[4]
Term baby	Mediastinal mass (teratom)	Fungemia	AMB	Survived	Colombia	[5]
Case 1 (50/M)	Large B cell lymphoblastic lymphoma Type 2 diabetes mellitus	Fungemia	AMB	Survived	India	[6]
Case 2 (Term baby)	Mother's vaginal infection with *K. ohmeri*	Fungemia	AMB	Survived		
9/M	Steroid resistant nephrotic syndrome, peritoneal dialysis Cyclosporine, chronic renal failure	Peritoneal fluid	Fluconazole AMB Caspofungin	Survived	Saudi Arabia	[7]
80/M	Colon carcinoma, chronic obstructive broncho pneumopathy	Fungemia	Fluconazole Liposomal AMB	Died	Italy	[8]
Premaure (33SA)/M	Mother: gravidic hypertension	Fungemia	AMB	Survived	France	[9]
69/M	Primary biliary cirrhosis	Fungemia Respiratory and urinary samples	Caspofungin □ Fluconazole	Died	France	[10]
43/M	Rhumatoid heart disease	Endocarditis Fungemia	Fluconazole (SDD) □ itraconazole	Survived	China	[11]
Case 1 (71/M)	Cellulitis Type 2 diabetes Coronary artery disease Iatrogenic Cushing's syndrome spine surgery	Fungemia	Fluconazole □ AMB deoxycholate	Survived	Taiwan	[15]
Case 2 (58/F)	oesophageal squamous cell carcinoma metastatic	Fungemia	Fluconazole	Died		
34/M	Immunocompetent Asthma Heavy alcohol use Tracheal-oesophageal fistula	Fungemia	Fluconazole (intermediate 16 mg/l) □ micafungin	Survived	USA	[17]
38/F	HIV seropositive	Oral lesion	Fluconazole	Loss to follow up	India	[12]
71/F	Type 2 diabetes mellitus, cellulitis	Fungemia Endocarditis Funguria	Fluconazole AMB deoxycholate	Survived	Taiwan	[13]
91/F	Rectosigmoidic ischemic necrosis (Hartmann)	Fungemia Urine Tracheal suction	Fluconazole	Died	France	[14]
75/M	Diabetes, hypertension, arrythmia,	Malignant external otitis: ear discharge Mastoid osteomyelitis: bone biopsy	AMB followed by Fluconazole	Died	Korea	[19]

Table 2: Clinical characteristics of 19 cases of *K. ohmeri* infections in the literature.

We also measured the susceptibility of the 3 isolates to various antifungal agents using the technique E-test®. The European Committee on antimicrobial susceptibility testing (EUCAST) recommendations does not indicate breakpoints [7]. CLSI has defined that antifungal susceptibility break points for this yeast are the same as those for Candida albicans isolates: Fluconazole MIC ≤ 2 µg/ml susceptible, 4 µg/ml dose-dependent susceptibility, and ≥ 8 µg/ml resistant. For caspofungin ≤ 0.25 µg/ml susceptible, 0.5 µg/ml intermediate and ≥ 1 µg/ml resistant with no category of for dose-dependent susceptibility. For amphotericin B, MIC ≤ 1 µg/ml susceptible and >1 µg/ml resistant [5,8]. Our three strains were resistant to caspofungin, susceptible-dose-dependent for fluconazole and susceptible for voriconazole and amphotericin B.

However, in literature there is no intrinsic resistance of *K. ohmeri* reported until now. Several cases of resistance to fluconazole and to echinocandin and only one case of amphotericin B resistance are reported [1,3,7,8,12,19,20]. Whereas, there is insufficient data to support a firm treatment recommendation [19].

The antifungal treatment described are mainly based on amphotericin B (or amphotericin B deoxycholate) with good response [6,19,21]. Furthermore, microbiological studies confirm the constant effectiveness of amphotericin B [6,12,19,21].

Fluconazole and itraconazole are moderately active and therapeutic failures are reported with fluconazole monotherapy [19]. Echinocandins are recently introduced but their use in infections with *K. ohmeri* is

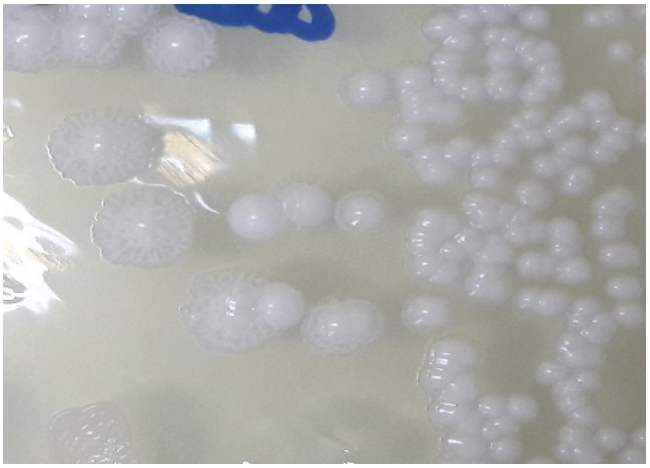

Figure 1: Macroscopic morphology of *K. ohmeri* grown at 37°C for 48 h on Chloramphenicol-Sabouraud dextrose agar (a: colony of *K. ohmeri*, b: colony of Candida albicans), Case N° 2.

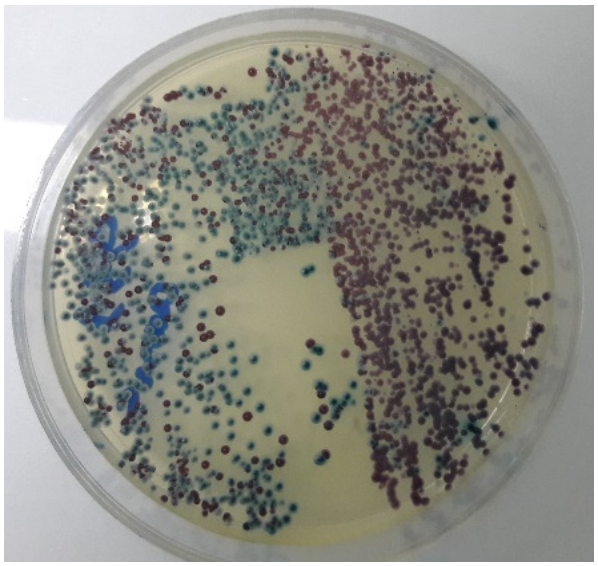

Figure 2: The color change of *K. ohmeri* cultured on CHROMagar *Candida* medium. The color of colonies has changed from pink to blue aroud day 2 and day 3, case N°3.

controversial. In fact, some studies demonstrate that infections were successfully treated with caspofungin or micafungin [2,3,8,10,13,21]. Whereas, our isolates were resistant with MIC for caspofungin >32 µg/ml. This joins the study of Janvier et al. (MIC caspofungin >16 µg/ml) [19], and of Lee et al. which described very low MICs for micafungin (0.03 to 0.06 mg/L) and MICs four times higher for caspofungin (0.125 to 0.25 mg/L) [17]. Ayaka et al. also reported high MIC for micafungin [1]. These data strongly support the recommendation to not use echincandins in *K. ohmeri* infections in first intention.

According to these studies, amphotericin B appears to be an attractive first line agent and echinocandins possibly promising alternative candidates. Antifungal susceptibility testing is recommended to guide treatment but also to provide MIC - outcome relationships and thus data for future optimised treatment recommendations [22].

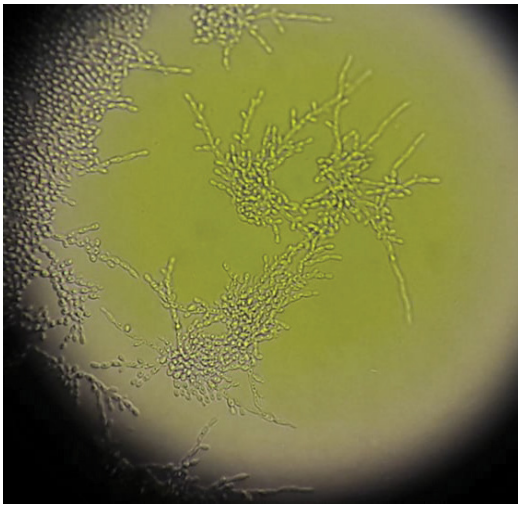

Figure 3: Pseudohyphae and balastoconidia of *K. ohmeri* after 24 hours of subculture on Tween Agar at 27°C.

Conclusion

Uncommon fungi like *K. ohmeri* are important opportunistic pathogens that may cause severe infectious disease in the immunocompromised hosts and other patients with risk factors. Favourable outcomes for this fungal infection are likely to be associated with early identification, effective antifungal therapy, and the removal of central venous catheters or medical devices. With the occurrence of drug-resistant strain, we should pay more attention to the use of antifungal drugs.

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