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Coinfection with Sars-Cov2 and *Kodamaea ohmeri*: A case report from Tunisia

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Abstract

Introduction: *Kodamaea ohmeri*, previously known as *Yamadazyma ohmeri* and *Pichia ohmeri*, is ascomycetous yeast that belongs to the *Saccharomycetaceae* family. It is a rare clinical isolate that has recently become known to cause various human infections. Here, we report the first case of co-infection with Sars-Cov2 and *Kodamaea ohmeri* in Tunisian patient without underlying disease.

Methodology: We describe a patient with Covid-19 where *Kodamaea ohmeri* was isolated in sputum and protected tracheal samples. 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: *Kodamaea ohmeri* was identified using phenotypic, biochemical, and molecular methods. The isolate was susceptible for amphotericin B, caspofungin, and intermediate sensitivity for Fluconazole.

Conclusion: Patients with severe Covid-19 are mostly colonized and co-infected with rare yeasts which are resistant to antifungals. This case incites to pay more attention to the emergence of this yeast.

Keywords: *Kodamaea ohmeri*; diagnosis; antifungal; molecular methods.

Introduction

Kodamaea ohmeri, previously known as *Yamadazyma ohmeri* and *Pichia ohmeri*, is an ascomycetous yeast that belongs to the *Saccharomycetaceae* family [4]. *Kodamaea ohmeri* is a rare clinical isolate that has recently become known to cause various human infections [9]. The first clinical isolation of *K. ohmeri* was made in 1984 from the pleural fluid of a patient from Java, but this isolate was regarded as a contaminant [5]. In Tunisia, the three firsts cases reported were resistant to antifungals which incite to pay more attention to the emergence of this yeast in human pathology [6]. In addition, this fungus is reported especially in patients with underlying immunosuppression such as hematologic or solid neoplasms use of immunosuppressive drug, type 2 diabetes mellitus and HIV seropositive [6]. However, its isolation in COVID-19 patients has not been reported in

the literature. Here, we report the first case of co-infection with Sars-Cov2 and *Kodamaea ohmeri* in Tunisian patient without underlying disease.

Case description

A 62-year-old patient with no underlying disease was admitted to the emergency (day 0) for dyspnea and fever at 38°C. SpO_2 in ambient air was at 87%. At arterial blood gas, the PaO_2 was 65 mmHg and the SaO_2 was 94%. The chest CT angiography showed an aspect of SARS-COV2 pneumonia with severe involvement estimated between 50 and 75%. In biological investigation, C-Reactive Protein (CRP) was 113 mg/L and D-dimers was 3176 ng/mL. The patient was put on oxygen therapy with a high concentration mask with antibiotic therapy based on Ceftriaxone and azithromycin and corticosteroid therapy as well as preventive anticoagulation with Enoxaparin 0.6 mL. On day +3, the SpO_2 decreased under 90% and the PaO_2 was 79 mmHg requiring the use of positive pressure ventilation alternating with ventilation by high concentration mask. On day +4, he was transferred to the intensive care unit. At admission, he was afebrile with stable hemodynamic constants. Blood culture, cytobacteriological and mycological examinations of urine and sputum, and protected tracheal samples are performed with stopping of azithromycin for treatment duration of 5 days and continuation of Ceftriaxone for 10 days.

Laboratory test results showed Creatinemia at 73 µmol/L, Urea at 5.6 mmol/L, CRP at 240 mg/L and Procalcitonin at 0, 29 µg/L. The buccal and nasal sites were colonized with *Candida* (C.) yeasts (*C. albicans, C. parapsilosis,* and *C. famata*). Mycological examination of the sputum and the protected tracheal sample revealed the presence of *Kodamaea ohmeri* yeasts. Thus, the patient was put on Voriconazole.

On day +7, he presented a respiratory distress with polypnea and an SpO2 of 60% requiring the tracheal intubation and the initiation of tazocillin and amiklin. In face of non improvement, the antibiotic therapy was changed on Day +11 to Imipeneme and vancomycin. His blood count showed moderate anemia (Hb = 11.6 g / dl), the D-dimer dropped to 1192 ng/mL with increased serum ferritin to 866 µmol/L. On day +16, the patient's condition deteriorated rapidly leading to death from severe sepsis post COVID-19 on the same day.

Methods

Sputum and the protected tracheal samples were cultured on Sabouraud medium, and CHROM agar medium (Beckton Dickinson, Paris, France). The identification was based on the results of the chlamydosporulation test on Tween agar medium, Vitek®2 compact (YST bio Merieux, 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 Mtibaa et al [6]. The analysis of the sequences was then done with the Blast tool. The antifungal susceptibility of the three isolates was determined by the guidelines of the Clinical and Laboratory Standards Institute (CLSI) by using RPMI 1640 medium and E test.

Results

Colonies on Sabouraud medium were creamy and smooth after 48 hours of incubation at 37°C. After 96 hours, they became radiated with a central dome (Figure 1). The quantification was greater than 10^2/ mL of dilution. On CHROM agar medium, the isolates produced pink-colored colonies which changed to blue after 48 h of incubation (Figure 2). On Tween agar, the strain showed small spores with tapering pseudofilamentation after 24 hours at 27°C (Figure 3). The isolate was identified *Kodamea (Pichia) ohmeri* by Vitek system (Bio Mérieux) after 24 hours.

The molecular identification showed that sequences matched in 99% with previous *K. ohmeri* in Gene Bank. The strain was sensitive to amphotericin B (MIC = 0.47 ug/ml), to caspofungin (MIC = 0.25 ug/ml) with intermediate sensitivity to fluconazole (MIC = 4 ug/ml).

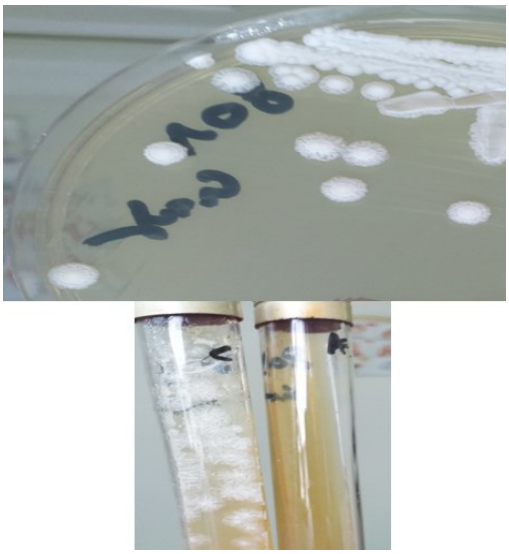

Figure 1: Colonies of kodmea ohmeri on sabauraud medium after 48 hours of incubation at 37°C.

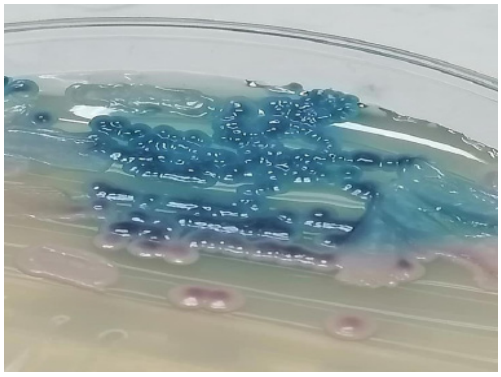

Figure 2: On CHROM agar medium, the isolates produced pink-colored colonies which changed to blue after 48 h of incubation.

Discussion

Kodamaea (Pichia) ohmeri belongs to the Ascomycetae class and is rarely occurring yeast that can be isolated from environmental sources, such as seawater, fruits, and pools [10]. The first isolate of *K.ohmeri* was reported in 1984 from a pleural fluid sample but it was considered a contaminant. In the same year, fungemia in a 48-year-old diabetic patient with immunosup-

pression due to renal transplantation was reported, who subsequently died from the infection [9]. Since then, more infections with this yeast have been reported considering it a true clinical pathogen, especially in patients with underlying immunosuppression [9,6]. Here, we reported first case of co-infection with Sars-Cov2 and *Kodamaea ohmeri* in Tunisian patient without underlying disease.

Table 1 summarizes shows that the majority of case reports are from Asia (Korea, Turkey, India), 23/36, 64%. There are a few descriptions from North America 7/36, 20%, some from Europe 6/36, 16%, and Arabic region (Turkey 2; Lebanon 1; Qatar 1; Kuwait 1). The largest series reported in the same site included 38 patients from a tertiary care hospital in North India, with 78.9% of these cases corresponding to neonates in intensive care units. In that series, the attributed mortality from this infection was 31.8%, but there are other reports of mortality as high as 50% in the pediatric population.

Table 1: Clinical characteristics of 36 cases of K. ohmeriinfections in the literature. [4]. (Kanno et al 2017).

Age/Gender	Background	Antifungal	Source	Outcome	Country	Year	Ref
48/F	DM, renal transplantation, steroids, CVC	FLZ then AMB	Fungemia	Died	USA	1998	[4]
71/M	DM, pacemaker, CVC, endocarditis	AMB	Fungemia	Died	Netherlands	2000	
42/M	IV heroin use, HCV	AMB and 5-FC	Endocarditis	Survived	Portugal	2002	
76/M	Prosthetic valve, PM	FLZ, then AMB	Endocarditis	Survived	USA	2002	
84/M	Right maxillary sinus SCC, CVC	FLZ, and then AMB	Catheter	Died	Japan	2002	
59/M	VP shunt infection, phlebitis	AMB	Fungemia	Survived	Korea	2003	
14/M	ALL, neutropenia, CVC	FLZ	Fungemia	Survived		2004	
8 month/M	Encephalitis, intravenous, catheter	FLZ	Fungemia	Died	Turkey	2005	
10/M	B cell-ALL, neutropenia, CVC	AMB	Fungemia	Survived		2005	
Neonate/F	Prematurity, necrotizing enterocolitis, intravenous catheter	FLCZ, AMB then liposomal AMB	Fungemia	Survived	USA	2006	
58/F	CML, CVC, chemotherapy	AMB	Fungemia	Survived	Brazil	2006	
11/M	Burkitt's lymphoma, neutropenia, CVC	FLZ	Fungemia + phlebetis	Died	Korea	2007	
41/M	Alcoholic ketoacidosis, TB, CVC	FLZ	Fungemia+ catheter	Survived			
47/M	DM, CRF, pneumonia, CVC	CVC removal, FLZ then AMB	Fungemia	Died			
4/f	Tetralogy of Fallot, CVC	FLCZ+AMB	Fungemia + catheter	Died			
Neonate/F	Prematurity, CVC	-	Fungemia	Survived			
82/F	DM, CRF, surgery	AMB	Fungemia	Died	Spain	2007	
5months /M	Short gut syndrome, hepatic insufficiency, broviac catheter	FLZ, AMB	Fungemia	Survived	USA	2007	
38/F	AML, hemochromatosis, chemotherapy, intravenous, catheter	AMB	Fungemia +catheter	Survived	Lebanon	2008	
3/F	Ascaris peritonitis, CVC, multiple antibiotics	liposomal AMB	Fungemia	Survived	Brazil	2009	
71/F	DM, tinea pedis, cellulitis	FLZ then AMB	Fungemia	Survived	Taiwan	2009	
Neonate/M	prematurity, arterial and venous catheter	AMB	Fungemia	Died	India	2009	
55/M	Alcoholic hepatitis, duodenal ulcer, CVC	FLZ then caspofungin	Fungemia	Survived	Taiwan	2010	
34/M	Asthma, alcohol abuse, thrombophlebitis, venous catheter, transesophageal fistula	Micafungin	Fungemia	Survived	USA	2010	
58/F	SCC of esophagus, nosocomial pneumonia, PICC	FLZ	Fungemia +catheter	Died	Taiwan	2010	
43/M	Rheumatic heart disease, endocarditid HBV carrier	ITZ	Endocarditis	Survived	China	2010	
Neonate/M	Enterocolitis, endocarditis, intravenous catheter	AMB	Endocarditis	Died	India	2011	
Neonate/F	Prematurity	AMB	Fungemia	Survived	Kuwait	2011	
46/M	Pneumonia, HBV carrier, MODS, CVC	FLZ then caspofungin,	fungemia	Survived	China	2013	
62/M	Gastric perforation, pneumonia, acute renal insufficiency, intravenous catheter	VRZ then AMB	Fungemia	Died			
75/M	Post total colectomy	AMB	Fungemia	Survived	India	2015	

80/M	AMI, retrocolic gastric bypass surgery, and splenectomy due to colon cancer, CVC, IABP	FLZ then L-AMB	Fungemia	Died	Italy	2015	
58/M	RA, acute pancreatitis, CVC	micafungin	Fungemia +catheter	Survived	Japan	2017	
81/M	Mild cognitive disorders	Caspofungin then voriconazol	Fungemia	Survived	France	2019	[2]
25/M	hypoxic-ischemic encephalopathy, pulmonary infection, and multiple organ dysfunction	Caspofungin	Catheter	Survived	China	2020	[13]
47/M	Diabetes	FLZ then L-AMB	Fungemia	Survived	Italia	2021	[14]

MIC: Minimum Inhibitory Concentration; AMB: Amphotericin B; FLCZ: Fluconazole; DM: Diabetes Mellitus; CVC: Central Venous Catheter; ND: No Data Reported; PM: Pacemaker; HCV: Hepatitis C Virus; SCC: Squamous Cell Carcinoma; VP Shunt: Ventriculoperitoneal Shunt; ALL: Acute Lymphoblastic Leukemia; CML: Chronic Myelogenous Leukemia; TB: Tuberculosis; CRF: Chronic Renal Failure; L-AMB: Liposomal Amphotericin B; PICC: Peripherally Inserted Central Venous Catheter; HBV: Hepatitis B Virus; ITCZ: Itraconazole; SDD: Susceptible Dose Dependent; MVR: Mitral Valve Replacement; TVP: Tricuspid Valve Plasty; MODS: Multiple Organ Dysfunction Syndrome; VRCZ: Voriconazole; AMI: Acute Myocardial Infarction; IABP: Intraaortic Balloon Pumping; RA: Rheumatoid Arthritis.

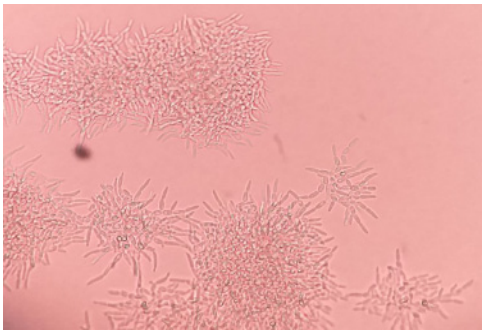

Figure 3: The microscopy of kodamea ohmeri colonies on a tween agar medium.

In the literature, the age of patients ranged from new born to 84 years old, the mean age was 42.6 years, 64.1% were males. Among the patients infected with *K. ohmeri*, 60.6% had already received an antibiotherapy treatment with antibiotics. All patients with infection of *kodemea ohmeri* have one or more underlying conditions or risk factors. They including are immunocompromised due to malignant hematological or solid tumors, post-chemotherapy neutropenia, immunosuppressive treatments, diabetes, or chronic renal failure [2]. The Majority were catheter-related and catheter removal was key to healing. Pre-exposure to systemic antibiotics was also reported in many cases. Systemic infections due to *K. ohmeri* are rarely reported in immunocompetent subjects.

For the isolation of *K. ohmeri*, blood cultures were used in 81.8% [9], cultures from nail specimens in 9.1%, and urine culture, peritoneal dialysis dialysate, oral swab, and deep wound infection in 2.7% each. On solid media, *K.ohmeri* forms *Candida*-like colonies and changes their color from pink to blue within 48 h on CHROM agar medium. Of the 5 species recognized in the *Kodamaea* genus, only *K.ohmeri* can grow at 37°C and cause human disease. Molecular diagnosis is available through the amplification and sequencing of the ITS2 region localized on the rRNA gene of the 5.8S and 28S subunit.

Our isolate in the present study was sensitive to AMB and caspofungin and had intermediate sensitivity to Fluconazole. The Literature reveals that *K. ohmeri* isolates have a low MIC for all antifungal agents except for a high range of MICs against fluconazole and caspofungin in some isolates [3,8]**.** Yuling et al 2013, found poor results in patients treated with fluconazole as the sole antifungal despite in vitro sensitivity. Treatment with amphotericin B, alone or in combination with flucytosine/fluconazole, produced more favorable results, with a survival rate of 66.7%. Echinocandin treatment was successful in 3 patients.

The study by Yang et al 2008 showed that the MICs of all isolates were sensitive to amphotericin B. Of the 13 antifungal susceptibility results available, seven isolates were sensitive to fluconazole (MIC 2.0 to 8, 0 mg/l) and six were intermediate including the remaining isolate (MIC 16.0 to 32.0 mg/l) [3,6,10].

Two cases in the pediatric intensive care unit were the first outbreak of *K. ohmeri* infection [1,8]. Both patients were infected with *K. ohmeri* sensitive to fluconazole (MIC 8.0 mg/l). One survived after treatment with amphotericin B, but the other died despite treatment with fluconazole. So far, all isolates of *K. ohmeri* are susceptible to amphotericin B [4,6,11]. Since amphotericin B is nephrotoxic in a dose-dependent manner, the use of a lower dose is preferred. However, in severely immunocompromised patients with systemic mycosis, a less favorable clinical outcome may result from the use of low doses of amphotericin.

The most common antifungals for the treatment of *K ohmeri* infections were amphotericin B in 59.5%, fluconazole in 35.1%, micafungin in 13.5%, voriconazole in 5,4%, and caspofungin and 5-flucytosine in 2.7% each, while 8.1% received no treatment [3].

According to the Clinical Practice Guidelines for the Management of Candidiasis from the Infectious Diseases Society of America, an echinocandin is recommended as initial therapy [12], (yuling et al 2013), fluconazole, the loading dose of 800 mg (12 mg/kg), then 400 mg (6 mg/kg) per day, is an alternative for patients who are not seriously ill and who have never been exposed to azoles.

Conclusion

K. ohmeri can cause life-threatening infections. Favorable results for this potentially fatal fungal infection are likely to be associated with early diagnosis and optimal antifungal regimens. Fluconazole is the least effective against *K. ohmeri* infections. Although more study is needed to establish the optimal antifungal regimens.

Declaration

Ethics approval and consent to participate: Not applicable.

Availability of data and materials: Not applicable.

Conflict of interest: This case report is not supported by any financial or personal interests.

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