Case Report

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A rare case of breakthrough fungal pericarditis due to fluconazole-resistant *Candida auris* in a patient with chronic liver disease

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Introduction: *Candida* pericarditis is a rare clinical entity with a high fatality, primarily attributed to difficulty in diagnosis. Unfortunately, the diagnosis is made post-mortem in more than 50 % of cases, and thus a high index of clinical suspicion is crucial.

Case presentation: We report a rare case of fungal pericardial effusion caused by the recently recognized multidrug-resistant *Candida auris*, which was cultured from pericardial fluid, blood, bronchoalveolar lavage and urine of a chronic liver disease patient while on empiric fluconazole therapy. The yeast was misidentified as *Candida haemulonii* by the VITEK2 commercial identification system, and was confirmed as *C. auris* by internal transcribed spacer and large ribosomal subunit sequencing. In addition, the VITEK2 AST card erroneously revealed a high amphotericin B MIC ($16 \mu\text{g ml}^{-1}$) and low caspofungin MIC ($0.25 \mu\text{g ml}^{-1}$) that did not correlate with results from the reference Clinical and Laboratory Standards Institute (CLSI) microbroth dilution method. Based on VITEK2 MIC data, the patient was administered caspofungin. However, *in vitro* antifungal susceptibility data for *C. auris* by the CLSI method exhibited high MICs to fluconazole ($64 \mu\text{g ml}^{-1}$) and caspofungin MIC ($1 \mu\text{g ml}^{-1}$) but low MICs to amphotericin B (MIC range, $0.125\text{--}0.5 \mu\text{g ml}^{-1}$). The patient's repeat pericardial fluid culture, despite caspofungin therapy for 12 days, grew *C. auris* and he died on day 13 of therapy.

Conclusion: *C. auris* is a recently reported agent of fungaemia and deep-seated infections and is notable for its antifungal resistance. Although early species identification and rapid antifungal susceptibility testing are needed in cases of critical infections, the reporting of rare yeast isolates exhibiting high MICs to antifungals by automated systems needs a cautionary approach.

Keywords: *Candida auris*; *Candida* pericarditis; caspofungin; fluconazole resistance; India.

Introduction

Candida pericarditis is a rare disease described mostly in patients with recent cardiothoracic surgery or debilitating chronic diseases, which is generally fatal and, unless treated, leads to impaired cardiac function. *Candida albicans* is the main aetiological agent but rarely other species such as *Candida tropicalis*, *Candida glabrata*, *Candida guilliermondii* and *Candida parapsilosis* have been reported (Schrack & Dooley, 1995; McNamee *et al.*, 1998; Neugebauer *et al.*, 2002). The overall mortality due to this clinical entity is significantly high (75 %) and is attributed primarily to difficulty in diagnosis because of the subtle clinical clues and insidious onset (McConnell & Robert, 1967; Rubin & Moellering, 1975; Kraus *et al.*, 1988). Here,

we report a rare case of fungal pericardial effusion caused by the recently described multidrug-resistant species *Candida auris* (Chowdhary *et al.*, 2014) in a patient with chronic liver disease (CLD). The present case also highlights the concern that this yeast had elevated MICs against commonly used antifungals and the patient had a fatal outcome, despite treatment.

Case report

A 43-year-old chronic alcoholic male, diagnosed to have CLD with decompensation evident by jaundice, ascites and deranged renal function for 2 months, was referred for liver transplant in June 2013. He had grade II hepatic encephalopathy, leucocytosis (total leukocyte count $23\,000 \mu\text{l}^{-1}$) with 88 % polymorphs and toxic granules in peripheral smear, total bilirubin 36.3 mg dl^{-1} , direct bilirubin of 23.2 mg dl^{-1} , coagulopathy with an international normalized ratio of 1.91 and deranged renal

Abbreviations: AMB, amphotericin B; CAS, caspofungin; CLD, chronic liver disease; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cut-off value; FLU, fluconazole; ITS, internal transcribed spacer; LSU, large ribosomal subunit.

parameters (blood urea nitrogen 133 mg dl⁻¹ and serum creatinine 3.6 mg dl⁻¹). Bacterial cultures of blood, sputum and ascitic fluid were negative. The patient was anuric with compensated metabolic acidosis. He was treated empirically with meropenem, colistin, haemodialysis IV albumin and fluconazole (FLU) 150 mg once a day for 2 weeks. Subsequently, 2 weeks after admission, he reported shortness of breath with cough and expectoration. On examination, both lower lung fields revealed bilateral coarse crepitations and a raised jugular venous pressure with tachycardia without hypotension. An electrocardiogram showed low voltage complexes and his chest X-ray showed bilateral consolidation, interstitial oedema and gross cardiomegaly with obliteration of cardiophrenic angle suggestive of pericardial effusion. The findings were confirmed on echocardiography and a significant amount of pericardial effusion with tamponade was observed. The patient was put on ventilator support, and pericardiocentesis was done. About 250 ml haemorrhagic fluid was drained and a sheath was placed *in situ* for further drainage. The pericardial fluid analysis showed a leukocyte count of 3600 µl dl⁻¹, with predominant polymorphs, and grew yeasts, which were identified as *Candida haemulonii*, by VITEK2 (BioMérieux). The antifungal susceptibility was performed using a VITEK2 AST Yeast card (BioMérieux), which revealed that the isolate had high MICs to FLU (32 µg ml⁻¹) and amphotericin B (AMB) (16 µg ml⁻¹) but low MICs to caspofungin (CAS) (0.25 µg ml⁻¹). *C. haemulonii* was also isolated from urine, blood and bronchoalveolar lavage. All the isolates were sent to a reference Medical Mycology centre for molecular identification. The patient was administered CAS, with a loading dose of 70 mg, followed by 50 mg daily. Although his bilirubin level decreased to 10 mg dl⁻¹ within 1 week, the derangement of renal parameters continued. His repeat pericardial fluid culture and urine grew *C. haemulonii* despite CAS treatment for 12 days. On day 13, his condition deteriorated and he finally succumbed to his illness due to septic shock. All four isolates from pericardial fluid, blood, bronchoalveolar lavage and urine developed a pink colour on CHROMagar *Candida* medium (Difco; Becton Dickinson) and showed ovoid to elongated budding yeast cells. Repeat identification by VITEK2 Compact (BioMérieux) and API20C (BioMérieux) misidentified them as *C. haemulonii* (96 % identity) and *Candida sake* (87 % identity), respectively. For molecular identification, genomic DNA was extracted as described by Xu *et al.* (2000). The internal transcribed spacer (ITS) region of the rRNA was amplified using established ITS-1/ITS-4 primers and the D1/D2 region of the large ribosomal subunit (LSU) using NL-1/NL-4 primers (White *et al.*, 1990; Kurtzman & Robnett, 1997). The amplified DNA was sequenced and GenBank BLAST searches were done for species identification. The ITS (GenBank accession nos KM000825–KM000827) and LSU (GenBank accession nos KM000828–KM000830) sequences showed 99 % homology with recently reported South African and Indian *C. auris* isolates sequences available in GenBank (ITS accession nos

KF689023.1, KJ126758.1 and KJ126759.1; LSU accession nos KC692056.1, KJ126763.1 and KJ126762.1). Also, LSU sequences of our *C. auris* isolates showed 99 % similarity with a Korean *C. auris* isolate (GenBank accession no. JX459779.1)

Antifungal susceptibility testing of the four isolates was performed in duplicate using the Clinical and Laboratory Standards Institute (CLSI) microbroth dilution method (CLSI, 2008). The MIC end points for azoles, AMB and echinocandins were read visually after 24 h, as validated recently by Pfaller *et al.* (2008, 2011). All four isolates had reduced susceptibility to FLU (MIC >64 µg ml⁻¹) and CAS (MIC 1 µg ml⁻¹). However, posaconazole (MIC ≤0.015 µg ml⁻¹), itraconazole (MIC range 0.03–0.125 µg ml⁻¹), voriconazole (MIC range 0.06–0.125 µg ml⁻¹) and 5-flucytosine (MIC range 0.125–4 µg ml⁻¹) exhibited potent activity. In addition, micafungin (MIC 0.06 µg ml⁻¹) and anidulafungin (MIC range 0.125–0.25 µg ml⁻¹) showed good activity. For all the isolates, the drugs tested revealed reproducible MICs when performed by different persons on two occasions revealing only a onefold difference in dilutions. The AMB and CAS susceptibility testing by VITEK2 was again repeated to check the reproducibility in the reference laboratory and revealed similar results of high (8–16 µg ml⁻¹) and low (0.25 µg ml⁻¹) MICs, respectively. The MIC values obtained by VITEK2 were in stark contrast to the data obtained using the CLSI method, which were reproducible on two occasions and revealed a high susceptibility to AMB (MIC range 0.125–0.5 µg ml⁻¹) and a low susceptibility to CAS (1 µg ml⁻¹) against all four isolates.

Discussion

This pericarditis case reported is unusual as it brings to the fore a rare diagnosis due to *C. auris* in a patient with CLD. *C. auris*, is a recently reported agent of fungaemia and deep-seated infections (Lee *et al.*, 2011; Chowdhary *et al.*, 2013, 2014). It is notable for its antifungal resistance and so far has been reported from Japan, Korea, India and South Africa (Kim *et al.*, 2009; Satoh *et al.*, 2009; Lee *et al.*, 2011; Chowdhary *et al.*, 2013, 2014; Magobo *et al.*, 2014). In the present case, the *C. auris* had elevated MICs to the empirically used antifungal (i.e. FLU) and exhibited a high MIC for CAS, which is a matter of concern, especially in patients in peritransplant settings. Similarly, breakthrough infections due to FLU-resistant *C. albicans*, *C. glabrata* and *C. krusei* in neutropenic and transplant recipient patients have been reported (Wingard *et al.*, 1991; Safdar *et al.*, 2001; Myoken *et al.*, 2003). Furthermore, not only was the yeast misidentified as *C. haemulonii* by a commercial identification system, but the high MIC of AMB and low MIC of CAS were also erroneously reported, therefore limiting the use of antifungals for patient management. The VITEK2 system is one of the most common automated systems used for identification and testing the susceptibility of clinically significant yeasts in routine

microbiology laboratories. However, the possibility of misidentification remains in this commercial identification system, particularly when rare species are reported. This may be attributed to the fact that the system attempts to generate identification of the rare species, which are not available in the existing database, rather than yielding no identification. Furthermore, isolates with antifungal resistance, particularly against azole-class agents, amphotericin and echinocandins, necessitate the accurate *in vitro* susceptibility testing of medically significant yeasts. It is noteworthy that *C. haemulonii* and *C. auris* differ in susceptibility to AMB, with *C. auris* being susceptible and *C. haemulonii* being remarkably resistant to AMB and azoles. Previously, false-positive resistance results for AMB by the VITEK2 system were reported for *C. lusitanae* and *C. kefyr* (Melhem *et al.*, 2014). In the present study, the high AMB MIC value for *C. auris*, as determined by the VITEK2 system, did not correlate with the results using the CLSI method, suggesting that future studies evaluating a larger number of *C. auris* isolates would further confirm our observations. Moreover, the antifungal susceptibility data for this rare species are limited, and only five reports, presented in Table 1, have been published (Kim *et al.*, 2009; Satoh *et al.*, 2009; Lee *et al.*, 2011; Chowdhary *et al.*, 2013, 2014). Although early species identification and rapid susceptibility testing are needed in cases of critical infections, the reporting of rare yeast isolates exhibiting high MICs to antifungals by automated systems needs a cautionary approach.

Previously reported predisposing factors for *Candida* pericarditis include thoracic surgery, malignancy, chronic steroids, diabetes, transplants, burns and catheter injury to the myocardium (Schrank & Dooley, 1995; McNamee *et al.*, 1998; Neugebauer *et al.*, 2002; Puius & Scully, 2007; Parikh *et al.*, 2009; Tang *et al.*, 2009). The majority of these patients, owing to underlying conditions, received broad-spectrum antibiotics leading to colonization by *Candida*, which can gain access to the mediastinum or bloodstream following invasive procedures. Our patient was a chronic alcoholic with decompensated liver disease, and had been on antibiotics for 2 weeks. Table 2 updates the cases of *Candida* pericarditis reported so far globally. *C. albicans* has been implicated in 47.5% of cases reported globally, followed by *C. tropicalis* (10%) and *C. glabrata* (5%); notably, in one-third of cases, species identification was not done. Overall, *Candida* pericarditis is often recognized late because of non-specific clinical symptoms and often-negative blood cultures for *Candida*. In the majority of the cases reviewed in Table 2, AMB remains the treatment of choice. Also, early pericardial drainage is essential for a successful outcome. In the present case, the initial empirical treatment with FLU for 2 weeks was followed by CAS, for which the isolate had a MIC of 1 µg ml⁻¹. Recently, the epidemiological cut-off values (ECVs) for the echinocandins were reported to be ≤0.25 µg ml⁻¹ for seven species. *C. glabrata*, *C. parapsilosis* and

Table 1. Antifungal susceptibility data of previously published *C. auris* isolates

Reference	No. isolates tested	Method of susceptibility	AMB	FLU	ITC	VRC	ISA	POS	CAS	MFG	AFG	FC
Satoh <i>et al.</i> (2009)	1	Not mentioned	–	2	0.06	0.03	–	–	–	–	–	0.5
Kim <i>et al.</i> (2009)	15	Etest method	0.38–1.5	2–128	0.125–4	0.03–2	–	–	0.125–0.25	0.03	–	–
Lee <i>et al.</i> (2011)	6	CLSI (2008)	0.5–1	2–128	0.125–2	0.03–1	–	–	0.06	0.03	–	–
Chowdhary <i>et al.</i> (2013)	12	CLSI (2008)	0.25–1	16–64	0.125–0.25	0.125–1	<0.015–0.25	0.06–0.25	0.125–0.5	0.125	0.125–0.25	0.06–0.125
Chowdhary <i>et al.</i> (2014)	15	CLSI (2008)	0.25–1	64	0.06–0.25	0.5–4	0.06–0.5	0.015–0.125	0.25–1	0.06–0.125	0.125–0.25	0.25–64
Present study	4	CLSI (2008)	0.125–0.5	>64	0.03–0.125	0.06–0.125	–	<0.015	1	0.06	0.125–0.25	0.125–4

ITC, itraconazole; VRC, voriconazole; ISA, isavuconazole; POS, posaconazole; FC, flucytosine; MFG, micafungin; AFG, anidulafungin.

Table 2. Global literature review on *Candida* pericarditis (1967–2014)

Reference (years), no. of cases	Sex/age	Underlying diagnosis	Species identification	Treatment and outcome
Schrank & Dooley (1995); (1967– 1995), <i>n</i> =25	13 M, 4 F, 8 unknown status/ 6 weeks– 77 years	Steroid therapy (<i>n</i> =4); CABG (<i>n</i> =3), DM (<i>n</i> =3); alcoholism (<i>n</i> =3); sternal wound infection (<i>n</i> =2); cardiac sternal OM (<i>n</i> =2); burn (<i>n</i> =2); chemotherapy (<i>n</i> =2); prolonged antibacterial therapy (<i>n</i> =2); malignancy (<i>n</i> =2); cardiac malformation repair (<i>n</i> =1); oesophageal rupture repair (<i>n</i> =1); oesophageal perforation repair (<i>n</i> =1); VSD repair (<i>n</i> =1); candidal oesophagitis (<i>n</i> =1); penetrating gastric ulcer (<i>n</i> =1); catheter-tip injury to myocardium (<i>n</i> =1); AVR (<i>n</i> =1); abdominal surgery (<i>n</i> =1); disseminated candidiasis (<i>n</i> =1); catheter-related fungaemia (<i>n</i> =1); VSD (<i>n</i> =1); ALL (<i>n</i> =1); HD (<i>n</i> =1); erythroleukaemia (<i>n</i> =1); COPD (<i>n</i> =1); SLE (<i>n</i> =1)	<i>C. albicans</i> (<i>n</i> =12), <i>C. tropicalis</i> (<i>n</i> =4), <i>Candida</i> sp. (<i>n</i> =10)	Administered AMB (<i>n</i> =10), 5-FC (<i>n</i> =2); death (<i>n</i> =19), cured (<i>n</i> =6)
Neugebauer <i>et al.</i> (2002) (1975– 2000), <i>n</i> =6*	3 M, 3 F, 4 weeks– 66 years	Truncus arteriosus and thymic hypoplasia (<i>n</i> =1); thoracoabdominal gastrectomy and oesophagojejunostomy (<i>n</i> =1); esophageal cancer (<i>n</i> =1); Heart transplant (<i>n</i> =1); BMT for aplastic anaemia (<i>n</i> =1); revision gastric bypass and cholecystectomy (<i>n</i> =1)	<i>C. albicans</i> (<i>n</i> =4); <i>C. glabrata</i> (<i>n</i> =1); <i>C. guilliermondii</i> (<i>n</i> =1)	Administered AMB (<i>n</i> =6), 5-FC (<i>n</i> =1); death (<i>n</i> =3), cured (<i>n</i> =3)
McNamee <i>et al.</i> (1998), <i>n</i> =1		Immunocompetent non-debilitated	<i>C. parapsilosis</i>	Surgery failed
Puius & Scully (2007), <i>n</i> =1		Heart transplant	<i>C. albicans</i>	Combination of CAS and FLU; cured
Tang <i>et al.</i> (2009), <i>n</i> =1	M, 47 years	Gastric adenocarcinoma	<i>C. albicans</i>	Antifungal therapy; cured
Parikh <i>et al.</i> (2009), <i>n</i> =1	F, 46 years	Polysubstance abuse, hepatitis C, DM	<i>C. glabrata</i>	7-week course of i.v. FLU; cured
Azhar (2012), <i>n</i> =1	F, 14 days	Premature birth with low weight	<i>C. albicans</i>	i.v. FLU (6 mg kg ⁻¹ day ⁻¹) and AMB lipid complex (10 mg kg ⁻¹ day ⁻¹) for 60 days; cured
Hensel <i>et al.</i> (2013), <i>n</i> =1	M	Drug abuse and acute lung injury	<i>Candida</i> sp.	Surgery and antifungal therapy; cured
Khoueiry <i>et al.</i> (2013), <i>n</i> =1	F, 76 years	Immunocompetent	<i>Candida</i> sp.	Surgery and antifungal therapy; cured
Present case, <i>n</i> =1	M, 46 years	CLD	<i>C. auris</i>	CAS (70 mg, then 50 mg daily for 2 weeks); died

M, male; F, female; ALL= acute lymphocytic leukaemia; AVR= aortic valve replacement; BMT= bone marrow transplant; CABG= coronary artery bypass graft; COPD= chronic obstructive pulmonary disease; DM= diabetes mellitus; 5-FC= flucytosine; FLU= fluconazole; HD= Hodgkin's disease; i.v., intravenous; OM= osteomyelitis; SLE, systemic lupus erythematosus; VSD= ventricular septal defect. *Twenty-five cases reviewed by Schrank & Dooley (1995) were overlapping and were not considered.

C. guilliermondii ECVs for echinocandins are $\leq 2 \mu\text{g ml}^{-1}$; however, no breakpoints or ECVs for rare *Candida* spp. such as *C. auris* have yet been published (Pfaller & Diekema, 2012). Moreover, Espinel-Ingroff *et al.* (2013) recently reported inter-laboratory MIC variations of CAS for *Candida* spp. using the CLSI method, which are similar to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC variations observed for the four common *Candida* spp. from seven laboratories. Furthermore, use of anidulafungin and micafungin MICs as markers for the echinocandins instead of CAS is recommended for making clinical therapeutic decisions (Arendrup *et al.*, 2011; Pfaller *et al.*, 2014). In our case, we could not demonstrate clinical

success with CAS, although the MICs with both the CLSI and VITEK2 methods were $\leq 1 \mu\text{g ml}^{-1}$. In addition, the failure of CAS administration in the eradication of *C. auris* is in consonance with previous reports demonstrating that this yeast is difficult to eradicate and causes persistent fungaemia despite therapy (Lee *et al.*, 2011; Chowdhary *et al.*, 2013, 2014). High mortality rates and therapeutic failure in 66 % of patients with *C. auris* infections have been reported (Chowdhary *et al.*, 2014). Finally, the importance of correct identification and standardized antifungal susceptibility testing for optimal management strategies of patients with invasive infections due to rarely emerging resistant *Candida* spp. can hardly be overemphasized.

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