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Earliest case of *Candida auris* infection imported in 2007 in Europe from India prior to the 2009 description in Japan

Marie Desnos-Ollivier [1]*, Arnaud Fekkar[2], and Stéphane Bretagne[1,3]

[1]Institut Pasteur, Molecular Mycology Unit, National Reference Center for Invasive Mycoses & Antifungal, UMR2000, CNRS, Paris, France

[2]Sorbonne Université, Inserm, CNRS, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, Service de Parasitologie Mycologie Groupe Hospitalier La Pitié-Salpêtrière, AP-HP

[3]Université Paris Diderot, Laboratoire de Parasitologie-Mycologie, Hôpital Saint Louis, AP-HP, Paris, France

*Corresponding author: Molecular Mycology Unit, Institut Pasteur, 28 rue du Docteur Roux, 75015, Paris, France. Email: mdesnos@pasteur.fr, phone number: +33(0)140613341, fax number: +33(0)145688420

Abstract (47 words)

Candida auris is an emerging pathogen frequently associated with multidrug resistance and involved in many worldwide outbreaks. We here report the first European imported case in France due to isolate belonging of the South Indian clade I and the importance of prevention measure to avoid fungal spreading.

Keywords:

Candida auris, Europe, India, whole genome sequencing, short tandem repeat

Case report (793 words)

Introduction

Candida auris has been under scrutiny because of several outbreaks reported in intensive care units (ICUs) [1, 2]. *Candida auris* was first described in a Japanese patient in 2009 [3], raising the hypothesis that the species was unnoticed before. Indeed, the earliest isolate of *C. auris* was found in 1996 in the Korean isolate collection [4]. However, the first European outbreaks date from spring 2015 [5, 6]. The French National Reference Center for Invasive Mycoses & Antifungals (NRCMA) provides expertise for difficult to identify isolates. We regularly review the isolates for which identification failed for lack of homology in the databases. This is how we discovered the oldest European isolate of *C. auris,* to date.

Clinical case

The patient, a 54-year-old male, had a long medical history with splenectomy in 1971 after traumatic shock and liver transplantation in 2004 followed by persistence of hepatitis C. He visited India in February 2007 for vacation. He was hospitalized in ICU for septic shock on April 11th in Delhi. Ultrasound investigation revealed a large liver abscess. Drainage yielded turbid bile but no germ. The patient was treated with (meropenem, ofloxacin, metrodinazole, and teicoplanine) and inotrope support (noradrenaline). The patient was repatriated in France on April 24th where antibiotics were pursued (imipenem, ciprofloxacine, teicoplanine and metronidazole in the hospital, followed by amoxicilline and metronidazole for a month at home). He was re-hospitalized in ICU on June 8th with cholestasis, renal insufficiency but without rejection on liver biopsy. Imaging showed several intrahepatic collections with arterial thrombosis. Cyclosporine was stopped and replaced by prednisone (5 mg/d) and mycophenolate mofetil. Caspofungin was added on June 10th on an empiric basis. On June 16th, a first extended-spectrum β-lactamase (ESBL) producing *Escherichia coli* was isolated from surveillance swabs leading to physical measures to prevent dissemination.

Hepatic drainage on June 28th yielded purulent liquid without bacteria but with an unidentified *Candida* sent to the NRCMA. Blood cultures were negative. Standardized EUCAST broth microdilution method for susceptibility testing of yeast revealed high minimum inhibitory concentrations (MIC) of fluconazole (≥64 mg/L) with lower values for voriconazole (0.5mg/L), posaconazole (0.125mg/L), amphotericin B (0.5mg/L), caspofungin (0.06mg/L) and micafungin (0.5mg/L) [2]. Caspofungin was stopped on July 7th The patient was given posaconazole 400 mg twice a day. The patient died 50 days after intensive cares.

Identification

Based on phenotypical identification (ID32C carbon assimilation pattern: 55671503151; bioMérieux, Marcy-l'Etoile, France) and internal transcribed spacers (ITS) of DNA ribosomal sequencing (Genbank accession number KP131674.1), using universal primers (V9D/LS266), the clinical isolate (CNRMA7.797), recovered from liver, was first identified as belonging to the *Candida haemulonii* complex. Recently, species identification was confirmed as *C. auris* upon ITS sequencing compared to sequence of the type strain (CBS 10913). Short tandem repeat (STR) genotyping, based on the 12 markers described by de Groot *et al.*, placed the isolate in the Indian clade I (STR genotype 17), the main genotype observed in the South Asian clade (Figure 1) [7, 8]. Whole genome of the clinical isolate was sequenced at the Mutualized Platform for Microbiology (P2M, Institut Pasteur, Paris, France), using an Illumina NextSeq 500 sequencer. Libraries were constructed using Nextera ® DNA Library Preparation Kit and sequenced using a 2 × 150 nucleotide paired-end strategy. All reads were preprocessed with AlienTrimmer v0.4.0. Genome was mapped to genome reference of each clade using the Burrows-Wheeler Alignment tool, BWA version 0.7.13 with the BWA-mem algorithm and SAMtools version 1.9. Single nucleotide polymorphism (SNP) positions were determined using vcftools version 0.1.13. Genome analysis showed only 1,165 SNPs difference between the genome of the CNRMA7.797 isolate and that of the

representative strains of the clade I (B8441), while 51,935 SNPs, 36,353 SNPs, and 130,749 SNPs were found for clade II (strain B11220), clade III (strain B11221) and clade IV (strain B11243), respectively. These results were comparable to those available in the literature, confirming the belonging of the CNRMA7.797 isolate to clade I [9].

Discussion

The present case shows that *C. auris* existed in 2007 in India before the first description [3] and highlights the importance of international travel in its spreading [7]. A recent study demonstrated that majority of patients with *C. auris* colonization, no longer had detectable *C. auris,* 12 months after discharge of the community setting. This confirms that isolation of the patient is useful as long as the carriage of *C. auris* lasts [10]. It is therefore of utmost importance to quickly identify infected patients and carriers by systematic identification of uncommon yeasts recovered from patients returning from endemic countries, and specially if ESBL-producing bacteria have been identified. Protecting measures to prevent ESBL-producing bacteria dissemination probably also prevented secondary *C. auris* cases in 2007 since no case was reported in France before 2018 [11]. More studies in endemic countries are warranted to assess the current prevalence of *C. auris* in patients but also in the environment.

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Figure 1: Minimum spanning tree of 40 representative STR genotypes described by de Groot

et al.[8], constructed using Bionumerics v6.1 (Applied Maths, Kortrijk, Belgium). Each circle represents a STR genotype with a clade-specific color (orange for clade I South Asia, yellow for clade II East Asia, blue for clade III Africa, green for clade IV South America, purple for clade IV Iran). The black circle corresponds to the clinical isolate CNRMA7.797, reported in the present study. The number of the STR genotype is indicated in each circle. The branch lengths indicate the similarity between isolates with the number of markers differing between genotypes.

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