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► To cite this version:

Marie Desnos-Ollivier, Arnaud Fekkar, Stéphane Bretagne. Earliest case of *Candida auris* infection imported in 2007 in Europe from India prior to the 2009 description in Japan. *Journal of Medical Mycology = Journal de Mycologie Médicale*, 2021, pp.101139. 10.1016/j.mycmed.2021.101139 . pasteur-03208437

HAL Id: pasteur-03208437

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Submitted on 26 Apr 2021

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

3

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17

18 **Abstract (47 words)**

19 *Candida auris* is an emerging pathogen frequently associated with multidrug resistance and

20 involved in many worldwide outbreaks. We here report the first European imported case in

21 France due to isolate belonging of the South Indian clade I and the importance of prevention

22 measure to avoid fungal spreading.

23 **Keywords:**

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

25

26 **Case report (793 words)**

27 **Introduction**

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

36 **Clinical case**

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

51 Hepatic drainage on June 28th yielded purulent liquid without bacteria but with an
52 unidentified *Candida* sent to the NRCMA. Blood cultures were negative. Standardized
53 EUCAST broth microdilution method for susceptibility testing of yeast revealed high
54 minimum inhibitory concentrations (MIC) of fluconazole (≥ 64 mg/L) with lower values for
55 voriconazole (0.5mg/L), posaconazole (0.125mg/L), amphotericin B (0.5mg/L), caspofungin
56 (0.06mg/L) and micafungin (0.5mg/L) [2]. Caspofungin was stopped on July 7th The patient
57 was given posaconazole 400 mg twice a day. The patient died 50 days after intensive cares.

58 **Identification**

59 Based on phenotypical identification (ID32C carbon assimilation pattern:
60 55671503151; bioMérieux, Marcy-l'Etoile, France) and internal transcribed spacers (ITS) of
61 DNA ribosomal sequencing (Genbank accession number KP131674.1), using universal
62 primers (V9D/LS266), the clinical isolate (CNRMA7.797), recovered from liver, was first
63 identified as belonging to the *Candida haemulonii* complex. Recently, species identification
64 was confirmed as *C. auris* upon ITS sequencing compared to sequence of the type strain
65 (CBS 10913). Short tandem repeat (STR) genotyping, based on the 12 markers described by
66 de Groot *et al.*, placed the isolate in the Indian clade I (STR genotype 17), the main genotype
67 observed in the South Asian clade (Figure 1) [7, 8]. Whole genome of the clinical isolate was
68 sequenced at the Mutualized Platform for Microbiology (P2M, Institut Pasteur, Paris, France),
69 using an Illumina NextSeq 500 sequencer. Libraries were constructed using Nextera® DNA
70 Library Preparation Kit and sequenced using a 2 × 150 nucleotide paired-end strategy. All
71 reads were preprocessed with AlienTrimmer v0.4.0. Genome was mapped to genome
72 reference of each clade using the Burrows-Wheeler Alignment tool, BWA version 0.7.13 with
73 the BWA-mem algorithm and SAMtools version 1.9. Single nucleotide polymorphism (SNP)
74 positions were determined using vcftools version 0.1.13. Genome analysis showed only 1,165
75 SNPs difference between the genome of the CNRMA7.797 isolate and that of the

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

80 **Discussion**

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

93

94 **Acknowledgments**

95 We thank the Mutualized Platform for Microbiology (P2M, Institut Pasteur, Paris,
96 France) for whole genome sequencing.

97 **Funding**

98 This work was supported by Institut Pasteur and Santé Publique France.
99 The authors have no conflict of interest.

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

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

108

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