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Case report

Tsukamurella inchonensis isolated from catheter of an Ecuadorian patient with hemodialysis

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ABSTRACT

We report a case of catheter-related bloodstream infection by *Tsukamurella inchonensis*, identified using 16S rRNA gene sequencing, in a patient with arterial hypertension for 20 years and chronic kidney disease in hemodialysis since 08/07/2019. To our knowledge, this is the first case of *T. inchonensis* in Ecuador.

Introduction

Tsukamurella is a strictly aerobic, Gram-positive and nonmotile bacterium, that is weakly or variably acid-fast and is included in the order *Actinomycetales. Tsukamurella* is an environmental organism that potentially causes various infections in humans. It has been isolated from deep-water marine sponges, activated sludge, and soil [1]. Human infections with *Tsukamurella* species are rare because the species is a kind of saprophyte bacterium; to date there has been no decisive report showing a specific virulence factor for this genus [2].

Most of the information related to human infection with *Tsukamurella* has been derived from case reports. Although bacteremia, peritonitis, meningitis, eye infections, cutaneous infections, brain abscess, respiratory tract infection, acute otitis media and catheter bloodstream infection have been identified as a source of infection, most cases have been related to the latter [3–6] in which it has been shown that the infection only resolved after removal of the catheter [7]. Mortality is very low and since infections caused by this bacterium are rare, it can be inferred that it is a kind of sporadic hospital infection [8].

Tsukamurella spp. consists of 11 recognized species but only five species have been isolated from human samples. These include *T. paurometabola* (type strain of the genus), *T. tyrosinosolvens*, *T. pulmonis*, *T. inchonensis*, and *T. strandjordae* [2–5]. To date, there are no firm conclusions about the best antibiotic therapy, which varied widely in terms of antibiotic choice and duration, and there are no cut-off points for antibiotics to establish the sensitivity or resistance of this bacterium.

We report a case of catheter-related bloodstream infection by *Tsukamurella inchonensis*, identified by Malditof and confirmed by using 16 S rRNA gene sequencing, in a patient with arterial hypertension for 20 years and submitted to hemodialysis. To our knowledge, this is the first case of *T. inchonensis* described in Ecuador.

Case

A 49-year-old woman was admitted to a hemodialysis private center in Santo Domingo de los Tsachilas city in Ecuador. She was diagnosed with arterial hypertension 20 years ago and has had a continuous treatment of a combination of alpha1-blockers antihypertensives (doxazocin 4 mg BID), angiotensin II receptor antagonist (losartan 150 mg OD) and a non- selective beta-adrenergic receptor blocker, (carvedilol 12.5 mg BID). She was treated for hypothyroidism with levothyroxine 50 mcg OD for 10 years. She has been on hemodialysis due to chronic kidney disease since 2019.

On October 20th, 2021, the patient who was a carrier of a left jugular tunneled catheter came to the clinic due to fever and chills

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after dialysis. Suspected infection of the hemodialysis catheter is why empirical antibiotic therapy based on vancomycin 500 mg was given after the hemodialysis session, amikacin 500 mg intravenously post-dialysis doses are indicated, showing clinical improvement. On November 3rd, she developed a fever (37.9 °C), but radiography did not identify any source of infection. The white blood cell count was 0.1×10^9 cells/liter, and the C-reactive protein level was 90 mg/liter. Empirical treatment was initiated with cefepime (4 g/day). After 3 days, her fever rose to 38.3 °C, and cefepime was therefore discontinued and replaced by meropenem (3 g/day) due to the fact that Gram-negative rods were seen in Gram stain and ESBL-*Klebsiella pneumoniae* was isolated. Upon treatment, the patient became afebrile, the C-reactive protein level decreased to 2.1 mg/liter, and the white blood cell count recovered to 1.7×10^9 cells/liter. On November 14th, a set of blood cultures were performed and *Tzukumarella inchonensis* was isolated. The fever was resolved within 3 days, and it was decided to relocate the tunneled catheter in the femoral region. Currently, the patient is in stable clinical conditions, on dialysis therapy. She was uneventfully discharged from the hospital.

Microbiological characteristics of strains

Two blood cultures were obtained, one from the peripheral vein and another through a catheter hub. BACTEC™ blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md) was used. A differential time of two hours to positivity was considered. Gram-positive rods were detected both in the peripheral blood culture and the blood obtained through the catheter hub. The specimens from the bottles were plated onto Chocolate Agar and MacConkey Agar, and these were incubated at 35 °C in 5% of CO_2 and ambient air respectively. After 48 h, yellowish, rough, dry, 2 mm in diameter, suede like appearance grew in both agars. Fig. 1. The colonies were found as catalase positive and oxidase negative. Strains were strictly aerobic, Gram-positive rods, weakly acid-fast, non-sporulated rods. The colonies were unidentifiable by routine microbiological examinations.

Fig. 1. Colonies of *Tsukamurella inchonensis* in Chocolate Agar. Note yellow, rough, irregular, flat, dry colonies with a suede like appearance.

The RapID CB Plus system (Remel Inc., Lenexa, KS, USA) was used for identification. The isolate was initially identified as *Rhodococcus equi*. As the colonies do not resemble a *Rhodococcus*, we proceeded to identify them by the BD Phoenix™ system using the Gram-positive panel. The device identified the bacteria as *Micrococus*, a Gram-positive coccus. As the two identifications were not adequate, we proceeded to sequence of the first 500-bp 16S rRNA gene aligned in the GenBank database enabling us to identify our isolates as belonging to *Tsukamurella* genus leading to a 100% match (753/753 bp) with *T. inchonensis* NCTC 10741 (GenBank accession number LR131273.1).

Susceptibility test

There are no cut-off points for this bacterium determined by an international organization to perform the susceptibility test. Some articles indicate that they have been based on the cut-off points for *Mycobacteria* and for *Corynebacterium*, however there are not enough studies for established cut-off points. For this reason, we performed microdilution broth to determine the MIC, using the commercial Sensititre™ Gram Positive MIC Plate (GPN3F) Thermo Scientific™ and the Sensititre™ RAPMYCO2 Susceptibility Testing Plate (RAPMYCO2). The results of susceptibility tests are shown in Table 1.

Discussion

According to the Yearbook of Health Statistics 2017, in Ecuador, health authorities estimate that nearly 10,000 people are undergoing hemodialysis and peritoneal dialysis treatment. It represents a rate of 660 cases per million Ecuadorians. In 2017, 20,182 discharges were registered in the health system of patients with kidney damage; 10,229 were due to kidney failure, and men were the most affected gender [9].

Although the recommended vascular access for the development of hemodialysis is the autologous arteriovenous fistula, more and more tunneled central venous catheters (CVC) are being used. Infection is the most common cause of morbidity, and the second cause of mortality in this population [10]. The colonization of the connections is the key in the etiopathogenesis of these infections. The diagnosis of bacteremia related to the catheter can be made using conservative techniques, such as paired quantitative blood cultures or conventional blood cultures extracted through CVC and venipuncture and the calculation of the differential time [10].

Long-term dialysis patients with tunneled catheters and bacteremia are a complex issue. Not only is the catheter the source of the infection but also the vascular access for providing ongoing dialysis therapy. There are 4 potential management options: (1) intravenous antibiotics alone, (2) prompt catheter removal with delayed placement of a new tunneled catheter, (3) exchange of the infected catheter with a new one over a guidewire, or (4) use of an antibiotic lock [11]. Administration of intravenous antibiotics alone is unsatisfactory because bacteremia recurs in approximately 75% of patients when the course of antibiotics has been completed [12,13]. Mokrzycki MH et al., observed a 5-fold greater risk of treatment failure in dialysis patients with catheter-related bacteremia that was treated with antibiotics alone compared with antibiotics and catheter removal [14].

Treatment will depend on the clinical situation of the patient, the microorganism involved and the presence of local infectious complications (tunnelitis) or systemic (endocarditis, suppurative thrombophlebitis, osteomyelitis) [11]. The patient was considered stable with an episode of bacteremia caused by a poorly virulent organism, similar to infections caused by a coagulase negative staphylococcus. To date, there has been no decisive report that shows a specific virulence factor for this *Tsukamurella* genus [2]. In this case,

Table 1
Minimal inhibitory concentrations (MICs) for *Tzukumurella inchonensis* isolated from blood and catheter hub.

Antimicrobial agent	MIC (ug/mL)	Interpretation
Chloramphenicol	16	R
Daptomycin	> 4	R
Linezolid	< 1	S
Trimethoprim/ sulfamethoxazole	< 0.25/4.75	S
Quinupristin/ dalfopristin	> 4	R
Erythromycin	4	R
Clindamycin	2	R
Clarithromycin	1	R
Ampicillin	> 8	R
Penicillin	> 8	R
Oxacillin*	> 4	R
Ceftriaxone	< 4	S
Vancomycin	1	S
Tetracycline	< 2	S
Doxycycline	1	S
Minocycline	< 1	S
Tigecycline	< 0.12	S
Ciprofloxacin	0.12	S
Levofloxacin	< 0.25	S
Moxifloxacin	< 0.25	S
Gentamicin	< 2	S
Amikacin	< 1	S
Tobramycin	2	S

R = resistant, S = Sensible

a systemic antibiotic treatment meropenem was combined with a local one (antibiotic lock). The patient started on intravenous antibiotic therapy without immediate catheter removal.

In an infectious process, the rapid and accurate identification of bacteria is vital in the diagnosis and treatment of infections. Many of the traditional phenotypic methods and commercial kits allow the identification of most of the bacterial species most commonly found in clinical microbiology laboratories [2]. However, these methods fail to identify *Tsukamurella* from other related genera of the order *Corynebacteriales* such as *Nocardia*, *Rhodococcus* and *Gordonia.* In most clinical microbiology laboratories, the identification of species within these genera is difficult, if not impossible, as they share similar phenotypic properties [2]. The only alternatives for an unequivocal identification of this genus are MALDI-TOF, polymerase chain reaction (PCR) and DNA sequencing or universal genetic target amplification and sequencing. MALDI-TOF should be useful for routine species identification of *Tsukamurella* in clinical microbiology laboratories. It must be ensured that the software is up to date for the identification of this genus, it cannot always identify all species [15].

In the absence of a cut-off point, it will not be possible to proceed with evaluation based on phenotypic tests unless a reliable and reproducible MIC value can be obtained for the isolate. If a MIC can be reliably determined, guidance can be provided. Disk broadcast or gradient strip such as E-test, cannot be used. In some cases, it is relevant to search the literature for advice on which antimicrobials to include in the test. We used two plates to perform MIC, one of Gram-positive cocci and the other of fast growth *Mycobacterium*. The analysis of the cut-off points was performed according to the ESCMID document: What to do when there are no clinical breakpoints [16].

The is lack of information about sensitivity to antibiotics in *Tsukamurella* spp. Generally, they are resistant to penicillin, oxacillin, piperacillin/ tazobactam and cephalosporins, which are prescribed for treatment of nontuberculous mycobacteria infection, whereas *Tsukamurella* is susceptible to amikacin, ciprofloxacin, imipenem, doxycycline, linezolid and sulfamethoxazole [2,17]. The combination of beta-lactam and aminoglycoside antibiotic agents for a long period has been recommended and the removal of catheters is the most important action for improved outcomes [17].

Although *Tsukamurella* infections have been increasingly reported in Europe, Asia, America, and Africa, indicating that diseases caused by this group of bacteria are emerging on a global scale, species identification within this genus is difficult in most clinical microbiology laboratories. To date, the alternative to identify this genus is MALDI-TOF and 16S rRNA PCR and sequence is a more reliable and rapid tool to identify *Tsukamurella* genus.

The best strategy to avoid catheter-related bloodstream infections is prevention. The fundamental preventive measure is asepsis in the CVC insertion and manipulation procedure.

Ethical statement

The research was approved by Comité de Ética de la Investigación en Seres Humanos of Pontificia Universidad Católica del Ecuador, code EO-36–2021.

Conflict of interest

None of the other authors have any potential conflict of interest to disclose.

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Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in Chief of this journal upon request.

CRediT authorship contribution statement

Jeannete Zurita: Conception and design of the work. Noriega Ana: Data collection. Pirela Oscar: Data collection. Cecibel González: Data collection. María Belén Solís: Drafting of the manuscript. Ariane Paz y Miño: Drafting of the manuscript. Jeannete Zurita: Drafting of the manuscript. María Belén Solís: Critical revision of the manuscript. Jeannete Zurita: Critical revision of the manuscript. Jeannete Zurita: Approval of its final version.

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