CASE REPORTS

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Emergence of Methicillin and Extensively Drug-Resistant *Staphylococcus pseudintermedius* in Türkiye: A Case of Urinary Tract Infection due to Urinary Stones in a Cat *

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The purpose of this case report is to present, for the first time, a case of extensively drug-resistant (XDR) and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in a cat, and to highlight the emergence of XDR-MRSP in companion animals. A three-year-old neutered mixed-breed male cat was presented to the animal hospital with anuria of 24 hours and dysuria, anorexia, and vomiting of approximately six months' duration. Clinical examination revealed high fever (39.6°C), stranguria, and hematuria. Urethrostomy revealed urethral obstruction due to struvite crystals. After culture and antimicrobial susceptibility testing, a feline lower urinary tract infection caused by XDR-MRSP was diagnosed. After treatment with florfenicol, the bacteria were successfully eradicated and clinical signs improved. This report presents the first documented case of XDR-MRSP in a feline patient. This case highlights the possibility of transmission of *S. pseudintermedius*, a canine commensal, through direct contact with a cat via the pet owner. It also reemphasizes the need for antimicrobial susceptibility testing, continuous monitoring of antimicrobial resistance, and the restriction of antimicrobial use in both humans and animals to limit the spread of XDR-MRSP in communities and hospitals and to establish appropriate treatment a protocol.

Key Words: *Staphylococcus pseudintermedius, methicillin, extensively drug-resistant, urinary tract infection, cat*

Türkiye'de Metisilin ve Yaygın İlaç Dirençli *Staphylococcus pseudintermedius*'un Ortaya Çıkışı: Bir Kedide Üriner Taşlara Bağlı İdrar Yolu Enfeksiyonu Olgusu

Bu vaka raporunun amacı, bir kedide yaygın ilaca dirençli (XDR) ve metisiline dirençli *Staphylococcus pseudintermedius* (MRSP) vakasını ilk kez bildirmek ve refakatçi hayvanlarda XDR-MRSP'nin ortaya çıkışını vurgulamaktır. Üç yaşında, kısırlaştırılmış, melez bir erkek kedi, 24 saat süren anüri ve yaklaşık altı aydır devam eden dizüri, anoreksi ve kusma şikâyetleriyle hayvan hastanesine getirildi. Klinik muayenede yüksek ateş (39.6°C), strangüri ve hematüri tespit edildi. Üretrostomide strüvit kristallerine bağlı üretral obstrüksiyon saptandı. Kültür ve antimikrobiyal duyarlılık testinin ardından, XDR-MRSP'nin neden olduğu bir kedi alt üriner sistem enfeksiyonu tanısı konuldu. Florfenikol tedavisinden sonra bakteri başarılı bir şekilde eradike edildi ve klinik bulgular düzeldi. Bu rapor, hasta bir kedide belgelenmiş ilk XDR-MRSP vakasını sunmaktadır. Bu vaka, bir köpek kommensali olan *S. pseudintermedius*'un hayvan sahibi aracılığıyla bir kediye doğrudan temas yoluyla bulaşma olasılığını vurgulamaktadır. Ayrıca, XDR-MRSP'nin toplumda ve hastanelerde yayılmasını sınırlamak ve uygun tedavi protokolü oluşturmak için antimikrobiyal duyarlılık testlerinin yapılmasının, antimikrobiyal direncin sürekli izlenmesinin ve hem insanlarda hem de hayvanlarda antimikrobiyal kullanımının kısıtlanmasının gerekliliğini bir kez daha ortaya koymaktadır.

Anahtar Kelimeler: *Staphylococcus pseudintermedius, metisilin, yaygın ilaç direnci, idrar yolu enfeksiyonu, kedi*

Introduction

Staphylococcus pseudintermedius is a well-documented canine pathogen that colonizes the skin and mucous membranes of dogs and is associated with infections of the skin, soft tissues, bones, and urogenital system (1, 2). Recently, this pathogen has received considerable attention due to reports of invasive human *S. pseudintermedius* infections (3, 4). Since both animal and human isolates of *S. pseudintermedius* have virulence and antimicrobial resistance characteristics similar to *Staphylococcus aureus*, this pathogen is considered a potentially significant emerging zoonotic threat (4).

The recent emergence of multidrug-resistant (MDR) *S. pseudintermedius* isolates, particularly methicillin-resistant *S. pseudintermedius* (MRSP) strains, poses a threat to the health of small animals. These isolates are increasingly being reported in veterinary clinics worldwide and are recognized as a significant canine health issue that limits treatment options due to their MDR phenotypes and challenges infection control measures. Furthermore, it raises public health concerns since it can be transmitted from animals infected and/or colonized with *S. pseudintermedius* to humans and is a zoonotic pathogen with the potential to cause life-threatening infections (3, 5-8). Humans typically acquire *S. pseudintermedius* through contact with infected or colonized dogs; this bacterium most commonly causes skin and soft tissue infections (SSTIs), particularly in immunocompromised individuals. Clinical manifestations include cellulitis, abscesses,

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wound infections, and lesions following dog bites. In more severe and less frequent cases, *S. pseudintermedius* may lead to invasive diseases such as bacteremia, endocarditis, osteomyelitis, sinusitis, otitis media, pneumonia, and prosthesis-associated infections (3, 6, 7). A feline case reported in Türkiye involved the isolation of a MRSP strain that was phylogenetically related to ST71 clones previously identified in dogs from various European countries and in a human case from the United States, highlighting both interspecies transmission and the global dissemination of MRSP (5). Furthermore, another case documented in a patient with rheumatoid arthritis demonstrated that an MRSP strain isolated from bone tissue was genetically similar to that of a household dog, providing strong evidence for direct zoonotic transmission from companion animals to humans (6).

Urinary tract infections (UTIs) constitute a serious health problem in companion animals that should not be underestimated. It has been stated that urine cultures are positive in 15-65% of dogs and up to 12% of cats presenting with clinical signs of UTI (9). Although UTIs are among the most common infectious diseases and are generally reported in dogs, there has been a significant increase in the documented incidence of UTIs in cats (9-11). *S. pseudintermedius* is a significant etiological agent of UTIs in dogs (12).

The databases Web of Science and PubMed were screened on March 21, 2024, using the following keywords: '*Staphylococcus pseudintermedius*' and 'extensively drug-resistant' or 'XDR' and 'cat' or 'feline' and 'urinary tract infection' or 'UTI' or 'feline lower urinary tract infection'. Although only one article was found as a result of these searches, this research article (13) did not explicitly state that extensively drug-resistant (XDR) was detected in the *S. pseudintermedius* isolate from cats. The search also did not reveal any other reports of extensively drug-resistant *S. pseudintermedius* in association with urinary tract infections in cats. This case report aims to describe the clinical and bacteriological features of urinary tract infection (UTI) caused by XDR-MRSP-associated urinary stones in a cat. To our knowledge, this is the first documented isolation of *mecA*-positive, XDR *S. pseudintermedius* from a cat with UTI, both in Türkiye and worldwide.

Case Presentation

A three-year-old, neutered, mixed-breed male cat presented to the clinic with anuria lasting 24 hours and dysuria, anorexia, and vomiting lasting approximately six months. According to the medical history, the cat had been taken to the veterinary clinic at regular intervals and prescribed antibiotics upon examination. It was also determined that the cat had lost 2 kilograms of weight due to its current health issues.

During the clinical examination of the cat, a high fever (39.6°C), dehydration, cachexia, stranguria, and hematuria were detected. The ultrasound examination revealed crystals in the bladder (Figure 1), a thickened bladder wall, and a dilated renal pelvis (Figure 2).

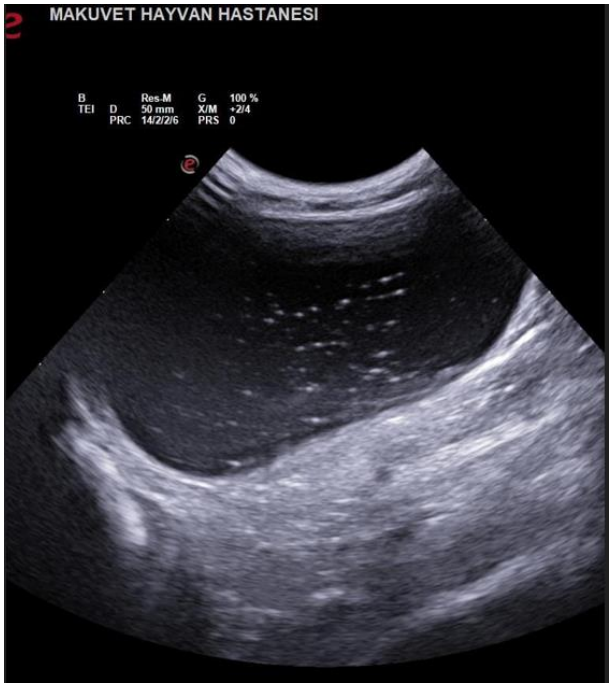

Figure 1. Appearance of crystals in the urinary bladder

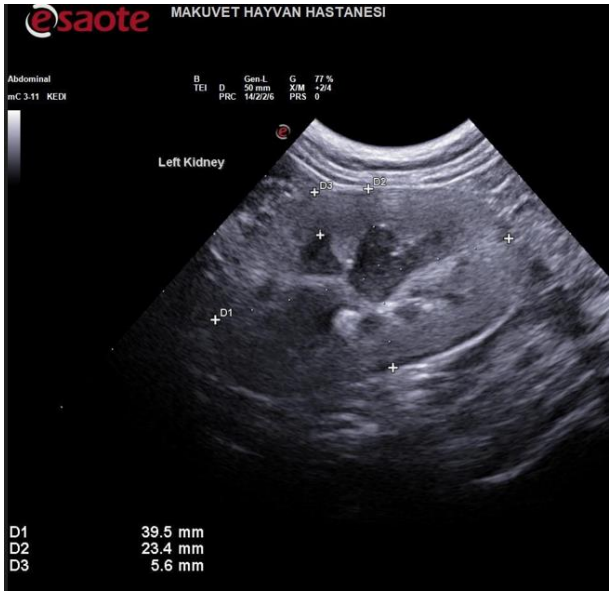

Figure 2. Renal pelvis dilatation

The serum biochemistry and hematology results indicated leukocytosis (31.94 X 10^9/L; reference range: 3.7–20.5 X 10^9/L), neutrophilia (27.16 X 10^9/L; reference range: 1.3–15.7 X 10^9/L), uremia (84.2 mg/dl; reference range: 20–65 mg/dL), hyperglycemia (159 mg/dl; reference range: 55-125 mg/dL), and a high serum creatinine level (2.28 mg/dl; reference range: 0.4-2 mg/dL). The remaining parameters were within the normal range.

The urethrostomy performed revealed a urethral stone blocking urine flow. The urinary stone was washed with 1 ml of sterile physiological saline in the direction of

the bladder using a sterile urinary catheter and then transferred to the urinary bladder. By promoting urine output, approximately 150 ml of urine was drained. Microscopic examination revealed numerous erythrocytes and struvite crystals (SCs). The biochemical urine examination indicated leukocyturia (70 leukocytes/µL; reference range: 0-15 leukocytes/µL) and hematuria (200 erythrocytes/µL; reference range: 0-10 erythrocytes/µL).

The urine sample obtained by urethrocytomy was sent to the laboratory for bacteriological examination. It was observed that the owner of the animal had wounds on her hands and nails. We learned that she is a manicurist. It was also learned that the cat lived at home and had no contact with any person or animal other than the owner. Because the owner did not give permission, samples could not be taken from her wounds.

Ten microlitres of urine were distributed onto blood agar (Oxoid, UK) containing 5% sheep blood and MacConkey agar (Condalab, Spain) plates. The plates were incubated at 37°C in an aerobic atmosphere. Following a 24-hour incubation period, β-haemolytic pure colonies were observed and assessed for catalase activity. Further analysis of the isolate via tube coagulase testing showed it was a coagulase-positive staphylococci (14). Identification of the isolate as *S. pseudintermedius* was conducted using matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Biotyper 3.0, Microflex LT: Bruker Daltonics GmbH, Bremen, Germany). DNA isolation was conducted using a commercial extraction kit, following the protocol provided by the manufacturer (Vivantis, Malaysia). To confirm the molecular identification of the isolate, the 16S rRNA gene region was amplified using the universal *27F* and *1492R* primers. The resulting bidirectional DNA sequence analysis (ABI 3730XL, Applied Biosystems, Foster City, CA) confirmed that the isolate was *S. pseudintermedius* (accession number PP506266). The bacterial concentration in the urine was found to be high, at $3x10^4$ CFU/mL.

Using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar (Merck), the antimicrobial resistance of *S. pseudintermedius* against the following 16 agents representing nine different classes was investigated: penicillin G (10 IU), ampicillin (10 µg) amoxicillin-clavulanic acid (20/10 µg), ceftiofur (30 µg), cefoxitin (30 µg), oxacillin (1 µg), gentamicin (10 µg), erythromycin (15 µg), tetracycline (30 µg), enrofloxacin (5 µg), ciprofloxacin (5 µg), clindamycin (2 µg), rifampin (5 µg), sulfamethoxazole/trimethoprim (SM/TM, 23.75/1.25 µg), chloramphenicol (30 µg), and florfenicol (30 µg). The results were interpreted according to the M100 and VET01 (2023) criteria of the Clinical and Laboratory Standards Institute (CLSI) (15). The isolate was resistant to all drug classes except the phenicol group antibiotics (chloramphenicol and florfenicol) and was categorized as XDR, as described by Magiorakos et al. (16). The presence of *mecA* gene was determined by polymerase chain reaction assay using specific primers (Forward: ACTGCTATCCACCCTCAAAC; Reverse: CTGGTGAAGTTGTAATCTGG) according to the protocol reported by Özdemir and Keyvan (17).

The treatment involved administering a total of 200 mL of balanced electrolyte solution at a rate of 5 mL/kg/hour daily, 1 mg/kg of furosemide (Lasix, Sanofi Aventis) twice a day, and ceftriaxone (Lesef, Ibrahim Etem) at a dose of 20 mg/kg intravenously twice a day. As part of the treatment, the bladder was washed using 50 mL of isotonic 0.9% NaCl. The diet was modified by applying Hill's Prescription Diet™ s/d™. A kidney supplement product (Ipakitine®) was administered to provide renal support. Based on the results of the antimicrobial susceptibility test (AST), the antibiotic was replaced with florfenicol (Flortek, Teknovet) administered at a dose of 20 mg/kg for seven days. After the treatment, the blood biochemistry level decreased to normal limits, clinical disease findings disappeared, and bacteriological recovery was achieved. Informed consent obtained from owner.

Discussion

Bacterial UTIs are one of the most common diseases in companion animals and are often treated empirically with antibiotics. According to recent reports, bacterial UTIs have been found to account for up to 63.7% of feline UTI cases (10, 11, 18, 19). Urolithiasis has been reported in 18-29% of cases of feline lower urinary tract disease (FLUTD) (18-21). According to many studies, the most frequently identified urolith is SCs in dogs and calcium oxalate crystals in cats (12, 19, 20, 22). It has been reported that UTIs caused by bacteria that produce the urease enzyme (*Staphylococcus* spp., *Escherichia coli*, and *Proteus mirabilis*) and the alkalinity of urine are mostly responsible for the formation of SCs in dogs (12), while nutritional, metabolic, and genetic factors are generally effective in the formation of SCs in cats (22).

S. pseudintermedius is an opportunistic pathogen that colonizes the skin and mucous membranes and causes various infections, especially in dogs rather than cats (1). *S. pseudintermedius* has been determined to be the most isolated bacterial agent among cases of UTIs and urolithiasis in dogs (12). However, *S. pseudintermedius* has rarely been reported among the causes of lower UTIs associated with urethral obstruction in cats (14, 23). It has been reported that animals with strivut crystals and urethral obstruction usually have a poor prognosis, the infection could not be treated, recurrent cases occurred, the patient's condition worsened, and the patient died or was euthanized (14, 19, 20).

In recent years, *S. pseudintermedius* has gained importance due to increased resistance to methicillin and non-β-lactam antibiotics. Methicillin-resistant staphylococci (MRS) show resistance to beta-lactam antibiotics as well as non-beta-lactam antibiotics, including lincosamides, aminoglycosides, quinolones, macrolides, phenicols, sulfonamides and tetracyclines (24). With the global rise in canine and feline MRSP or MDR cases of *S. pseudintermedius*, only a few cases of XDR in dogs and environmental samples have been

reported (18, 25, 26). However, no data are available on MRSP-XDR *S. pseudintermedius* in cats. To the best of our knowledge, MDR-MRSP has only been reported in a cat with otitis externa in Türkiye (5). However, there is no sufficient data on methicillin resistance in staphylococci isolated from the urine cultures of cats and dogs globally (14, 18, 23). This substantial increase in the prevalence of MDR-MRSP over time presents a serious situation that limits treatment options. Wettatein et al. (14) stated that they decided to euthanize a cat in which MRSP was isolated from a UTI due to the worsening of the infection. In this case, however, a cat with recurrent bacterial FLUTD, SCs and urethral obstruction caused by XDR-MRSP was rescued with an appropriate treatment protocol with florfenicol, the only antimicrobial agent identified as a suitable treatment option after AST, and no recurrent urinary problems were observed for the following 2 years.

MRSP infections have been reported to have high zoonotic and zooanthroponotic potential. In cases of persistent or recurrent human infections, domestic animals are recognized as potential MRSP reservoirs. Many studies have demonstrated zoonotic transmission of *S. pseudintermedius* and MRSP from dogs to humans. Direct contact between dogs and humans is reported to be an important factor in this transmission. MRSP strains are often multi-drug resistant, compromising treatment of infections and posing a public health concern. In recent years, invasive *S. pseudintermedius* infections in humans have been reported. It has also been reported that humans colonized with *S. pseudintermedius* may play a role in transmission between animals (1, 2, 7, 27). In this case, although samples could not be obtained from the wounds on the owner's hands, it was thought that the owner may have played a role in the isolation of *S. pseudintermedius*, a well-known commensal bacterium of dogs, from a cat.

In conclusion, this case highlights the presence of XDR-MRSP in cats, both in Türkiye and worldwide, and provides new insights into the antimicrobial resistance profile in Türkiye. Additionally, this case illustrates the significant risks associated with zoonotic and zooanthroponotic transmission of XDR-MRSP, along with the concerning potential for the transfer of antibiotic resistance. Furthermore, this report describes the first case of XDR-MRSP associated with FLUTD. We emphasize that AST and treatment protocols using appropriate antibiotics can save lives and provide clinical and bacteriologic cures even in such severe infections. The prevalence of MRSP in companion animals is unknown, and the emergence of MDR and XDR strains is of great concern. These strains cause not only treatment difficulties but also pose serious risks, being regarded as "One Health" problem, due to their ability to transfer antibiotic resistance to other pathogenic bacteria and cause severe infections in humans as zoonotic pathogens. To effectively limit the spread of *S. pseudintermedius* in society and hospitals and to improve the health of infected animals, it is essential to identify appropriate antibiotics and continuously monitor antimicrobial resistance through AST. National-level antimicrobial surveillance in various countries can inform and guide local antibiotic use policies, contributing to more effective management of antimicrobial resistance. Moreover, to effectively control of antibiotic resistance, local authorities should restrict and monitor the use of antibiotics in both humans and animals, and limit the use of the same antimicrobial agents in both human and veterinary medicine.

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