IDCases 7 (2017) 48–52

Contents lists available at ScienceDirect

IDCases

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Case report

Human case of bacteremia caused by *Streptococcus canis* sequence type 9 harboring the *scm* gene

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ARTICLE INFO

Article history:
Received 25 November 2016
Accepted 18 January 2017

Keywords:
Streptococcus canis
scm gene
Sequence type 9
Human case
Bacteremia

ABSTRACT

Streptococcus canis (Sc) is a zoonotic pathogen that is transferred mainly from companion animals to humans. One of the major virulence factors in Sc is the M-like protein encoded by the *scm* gene, which is involved in anti-phagocytic activities, as well as the recruitment of plasminogen to the bacterial surface in cooperation with enolase, and the consequent enhancement of bacterial transmigration and survival. This is the first reported human case of uncomplicated bacteremia following a dog bite, caused by *Streptococcus canis* harboring the *scm* gene. The similarity of the 16S rRNA from the infecting species to that of the Sc type strain, as well as the amplification of the species-specific *cfg* gene, encoding a co-hemolysin, was used to confirm the species identity. Furthermore, the isolate was confirmed as sequence type 9. The partial *scm* gene sequence harbored by the isolate was closely related to those of other two Sc strains. While this isolate did not possess the *erm*(A), *erm*(B), or *mef*(A), macrolide/lincosamide resistance genes, it was not susceptible to azithromycin: its susceptibility was intermediate. Even though human Sc bacteremia is rare, clinicians should be aware of this microorganism, as well as *Pasteurella* sp., *Prevotella* sp., and *Capnocytophaga* sp., when examining and treating patients with fever who maintain close contact with companion animals.

Introduction

Streptococcus canis (Sc) is a zoonotic pathogen that is transferred primarily from companion animals such as dogs and cats to humans through both animal bites and other mechanisms, and usually infects immunocompromised rather than immuno-competent hosts. This species has also been isolated from a variety of other animals, including cows, rats, mink, mice, rabbits, and foxes [1]. Sc strains are β-hemolytic, and they appear as large white colonies surrounded by zones of complete hemolysis when cultured on sheep blood agar plates. Furthermore, Lancefield grouping, based on the composition of carbohydrate antigens in the cell wall, was used to classify Sc as a group G streptococcus. The filamentous M protein is a major somatic virulence factor in group A streptococci, and the M-like protein produced by Sc strains is thought to play a similar role in Sc [2]. We present the first reported human case of uncomplicated bacteremia following a dog bite, caused by Sc harboring the *scm* gene, which encodes M-like protein. Furthermore, we review published reports of the clinical and microbiological characteristics of Sc infection in humans.

Case report

A 71-year-old man was admitted to our hospital with swelling and redness in his right leg, complicated by fever and rigor. His underlying medical conditions included atrial fibrillation, hypertension, superior mesenteric vein thrombosis, liver cirrhosis (LC) following infection with Hepatitis C Virus. He had received a splenectomy for splenomegaly due to LC. One year prior to admission, he had received the non-conjugated, pneumococcal polysaccharide vaccine because of the splenectomy. The patient was the owner of a dog that had become sick and had bitten his

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http://dx.doi.org/10.1016/j.idcr.2017.01.002

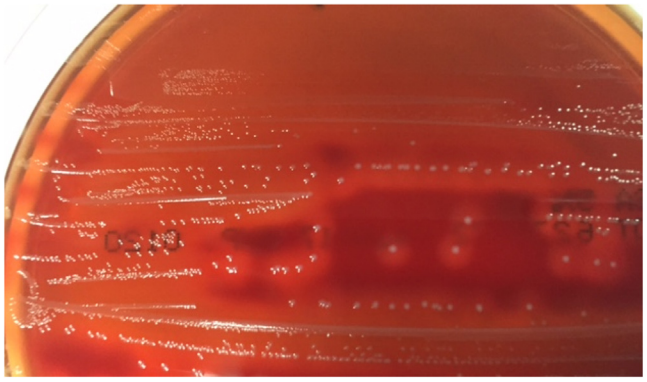

Fig. 1. Morphological features of large, smooth, white, non-mucoid β-hemolytic colonies of *Streptococcus canis*. The microorganism was cultured on a sheep blood agar plate for 24 h at 35 °C in 5% CO_2.

right leg several days previously. On admission to the emergency room, the patient exhibited a temperature of 40.2 °C, blood pressure of 150/110, a respiratory rate of 25 breaths/min, and an oxygen saturation of 94% (equivalent to the ambient concentration), and he was tachycardic with a heart rate of 106 bpm. The clinical examination was unremarkable with the exception of a systolic murmur (Levine II/VI) at the apex and the remarkable swelling and redness of his right leg. The leukocyte cell count and C-reactive protein concentration were 8500/μL and 0.30 mg/dL, respectively. Transthoracic echocardiography showed no evidence of vegetation that might indicate endocarditis, and a computed tomography scan of the chest, abdomen, and pelvis revealed no evidence of infective foci.

Cellulitis was diagnosed and the intravenous administration of the antibiotic cefmetazole was initiated (4 g per day, administered as two 2-g doses); however, concerns about severe infection were raised, because he had undergone a splenectomy. After admission, duplicate blood cultures revealed the presence of gram-positive cocci, and the cefmetazole treatment was replaced by the combined intravenous administration of ampicillin (12 g per day, administered as six 2-g doses) and clindamycin (1800 mg per day, administered as three 600-mg doses). The patient-origin samples were cultured on a sheep blood agar plate for 24 h at 35 °C in 5% CO_2, resulting in the growth of large, smooth, white, non-mucoid β-hemolytic colonies with group G carbohydrate antigens (Fig. 1).

The infecting species was matched to Sc with 99.9% probability, using a Rapid ID 32 Strep API system (SYSMEX bioMérieux Co. Ltd., Tokyo, Japan) to assess its biochemical parameters. Unfortunately, the dog died from the disease and the Sc strain could not be isolated from the dog. The isolate from the patient was stored at −80 °C for further characterization.

In summary, the patient was diagnosed with uncomplicated bacteremia caused by Sc, and was treated with a 2-week course of combined ampicillin and clindamycin therapy at set doses. The treatment was successful, and the patient remained well with no recurrence of bacteremia during the 4-month follow-up period.

Microbiological analyses

The phenotypic and genotypic characteristics of the isolate were determined, and are summarized in Table 1. The identification of the isolated species as Sc was confirmed by sequencing the 16S rRNA (read length 1426 bp); the isolate displayed 99.02% identity to Sc strain ATCC 43496(T). Furthermore, it was possible to amplify the *cfg* gene, encoding a CAMP factor co-hemolysin found in Sc [3], from the extracted DNA. Additionally, it was possible to detect the presence of a *scm* gene, encoding the major virulence factor M-like protein [4]; the amplified sequence (read length

Table 1
Phenotypic and genotypic characteristics and antimicrobial susceptibility results of *Streptococcus canis* isolate from a human case.

Phenotypic and genotypic parameters	Strain TA4
Clinical specimen	Blood
Gross appearance of colonies on a sheep blood agar plate	Non-mucoid, beta-hemolytic large-size white smooth colonies
Carbohydrate group (Lancefield antigen)	G
Numerical profile using the Rapid ID 32 Strep API system (% identification)	57116441 (99.9)
Similarity (%) to *S. canis* type strain[a] using 16S rRNA sequencing (sequencing size, bp)	99.02 (1426)
Amplification of *cfg* gene encoding a co-hemolysin, CAMP-factor	Positive
Amplification and sequencing of *scm* gene encoding M-like protein (sequencing size, bp)	Similarity to those of *S. canis* strains 321 324A and 341 4291B[b] (912)
Sequence type (allelic profile: *gki-gtr-murI-mutS-recP-xpt-yqiZ*)	9 (3-5-3-3–1-2-3)
Non-susceptible antimicrobial agent[c]	Azithromycin alone
Macrolide/lincosamide resistance determinant	None
Antimicrobial agents	Minimum inhibitory concentration (μg/mL)
Penicillin G	≤0.03
Ampicillin	≤0.06
Amoxicillin/clavulanic acid	≤0.25
Cefotiam	≤0.5
Cefotaxime	≤0.12
Ceftriaxone	≤0.12
Cefepime	≤0.5
Cefozopran	≤0.12
Cefditoren pivoxil	≤0.06
Meropenem	≤0.12
Erythromycin	≤0.12
Azithromycin	1
Clindamycin	≤0.12
Minocycline	≤0.5
Chloramphenicol	≤4
Vancomycin	0.5
Levofloxacin	0.5
Sulfamethoxazole-trimethoprim	≤0.5

[a] *S. canis* ATCC 43496(T).
[b] *Scm* accession numbers of strains 321 324A and 341 4291B were KF662395.1 and KF662396.1, respectively.
[c] Resistance to antimicrobials was determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute document M100-S22.

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TA4             GAGCAGCTACCACAACAACTGTAAAGGCAGAAAGTAATAGGGCTGATAGGGCAAGAATGG 60
321 324A        GAGCAGCTACCACAACAACTGTAAAGGCAGAAAGTAATAGGGCTGATAGGGCAAGAATGG 60
341 4291B       GAGCAGCTACCACAACAACTGTAAAGGCAGAAAGTAATAGGGCTGATAGGGCAAGAATGG 60
                ************************************************************

TA4             AAGTCTTATTAAAGTATGTGCCGTATGTTTCTTCTAATTACTGGTACCAGGAAGTACTTA 120
321 324A        AAGTCTTATTAAAGTATGTGCCGTATGTTTCTTCTAATTACTGGTACCAGGAAGTACTTA 120
341 4291B       AAGTCTTATTAAAGTATGTGCCGTATGTTTCTTCTAATTACTGGTACCAGGAAGTACTTA 120
                ************************************************************

TA4             AAAATGATGCACTGCGAGAAGAAGTGCAACGTTTAGAAGATTTAGTTGAATCAGAAGTAA 180
321 324A        AAAATGATGCACTGCGAGAAGAAGTGCAACGTTTAGAAGATTTAGTTGAATCAGAAGTAA 180
341 4291B       AAAATGATGCACTGCGAGAAGAAGTGCAACGTTTAGAAGATTTAGTTGAATCAGAAGTAA 180
                ************************************************************

TA4             AAGATTACAATGCTCTACTCGACAAGAAAGAATCCGTTGAAAAGCAGCTTAAGAGAACAG 240
321 324A        AAGATTACAATGCTCTACTCGACAAGAAAGAATCCGTTGAAAAGCAGCTTAAGAGCACAG 240
341 4291B       AAGATTACAATGCTCTACTCGACAAGAAAGAATCCGTTGAAAAGCAGCTTAAGAGAACAG 240
                ************************************************************ ****

TA4             AGGACAGCTTAGAAGTAACTGAAAAAGCTAACAAAGGTCTTACTAAAGAAAGAGATCTTT 300
321 324A        AGGACAGCTTAGAAGTAACTGAAAAAGCTAACAAAGGTCTTACTAAAGAAAGAGATCTTT 300
341 4291B       AGGACCGCTTAGAAGTAACTGAAAAAGCTAACAAAGGTCTTACTGAAGAAAGAGATCTTT 300
                ***** ************************************* ***************

TA4             TAACAGATTCTTTAGAAACCACCAAAAAAGCTCTTGAAGATAGCCAAAAAGAAGTTCAAG 360
321 324A        TAACAGATTTTTTAGAAACCACCAAAAAAGCTCTTGAAGATAGCCAAAAAGAAGTTCAAG 360
341 4291B       TAACAGATTCTTTAGAAACCACCAAAAAAGCTCTTGAAGATAGCCAAAAAGAAGTTCAAG 360
                ********* ************************************************

TA4             CTAACCTTGACGCTTTGAACCATAAGAACGAGCAAATTGCCAGCTTAGTCGGTGAAAGAG 420
321 324A        CTAACCTTGACGCTTTGAACCATAAGAACGAGCAAATTGCCAGCTTAGTCGGTGAAAGAG 420
341 4291B       CTAACCTTGACGCTTTGAACCATAAGAACGAGCAAATTGCCAGCTTAGTCGGTGAAAGAG 420
                ************************************************************

TA4             ATAGCTTGTCAGCACAACTATCTGCTAGCCAAGAGCGTAACGCTGAGTTGGAGCGTAACC 480
321 324A        ATAGCTTGTCAGCACAACTATCTGCTAGCCAAGAGCGTAACGCTGAGTTGGAGCGTAACC 480
341 4291B       ATAGCTTGTCAGCACAACTATCTGCTAGCCAAGAGCGTAACGCTGAGTTGGAGCGTAACC 480
                ************************************************************

TA4             TTGAAAGCTACGACCGCTTGATTGAGTCTGCAAAATTTGAAATGCAACAAAAACTAGCAG 540
321 324A        TTGAAAGCTACGACCGCTTGATTGAGTCTGCAAAATTTGAAATGCAACAAAAACTAGCAG 540
341 4291B       TTGAAAGCTACGACCGCTTGATTGAGTCTGCAAAATTTGAAATGCAACAAAAACTAGCAG 540
                ************************************************************

TA4             AAATTGAGCGCTTGACAGCTGAAAATGCAGACGCAAAAGATCAAATCGAGAAACTTCAAG 600
321 324A        AAATTGAGCGCTTGACAGCTGAAAATGCAGACGCAAAAGATCAAATCGAGAAACTTCAAG 600
341 4291B       AAATTGAGCGCTTGACAGCTGAAAATGCAGACGCAAAAGATCAAATCGAGAAACTTCAAG 600
                ************************************************************

TA4             CAGAAGTGTCAACACTTCGTGATCAAGTAGCAAGCCTAGACCGCTTGGTTGAATCAGCTA 660
321 324A        CAGAAGTGTCAACACTTCGTGATCAAGTAGCAAGCCTAGACCGCTTGGTTGAATCAGCTA 660
341 4291B       CAGAAGTGTCAACACTTCGTGATCAAGTAGCAAGCCTAGACCGCTTGGTTGAATCAGCTA 660
                ************************************************************

TA4             AGTATGACCTAGCTCAAAAACAAGCTGAAATCGATACCCTTACAAAACAAAAAGCAGAGG 720
321 324A        AGTATGACCTAGCTCAAAAACAAGCTGAAATCGATACCCTTACAAAACAAAAAGCAGAGG 720
341 4291B       AGTATGACCTAGCTCAAAAACAAGCTGAAATCGATACCCTTACAAAACAAAAAGCAGAGG 720
                ************************************************************

TA4             CAGAGCAAGCTCTTGCCGCAGAGCAAGCTAAAGTAGCTGAGCTTGAAAAACAACTTGAAG 780
321 324A        CAGAGCAAGCTCTTGCCGCAGAGCAAGCTAAAGTAGCTGAGCTTGAAAAACAACTTGAAG 780
341 4291B       CAGAGCAAGCTCTTGCCGCAGAGCAAGCTAAAGTAGCTGAGCTTGAAAAACAACTTGAAG 780
                ************************************************************

TA4             CATCAAACGCTAAAGTAGCTGAGCTTGAAAAACAAAAAGCAGAAGCAGAAGCTAAGATTG 840
321 324A        CATCAAACGCTAAAGTAGCTGAGCTTGAAAAACAAAAAGCAGAAGCAGAAGCTAAGATTG 840
341 4291B       CATCAAACGCTAAAGTAGCTGAGCTTGAAAAACAAAAAGCAGAAGCAGAAGCTAAGATTG 840
                ************************************************************

TA4             CTGTTCTTGAAAAAGACCTTGAAACAGCTCAAGCTGAAAACGCTAAGTACAAAGAACAAT 900
321 324A        CTGTTCTTGAAAAAGACCTTGAAACAGCTCAAGCTGAAAACGCTAAGTACAAAGAACAAT 900
341 4291B       CTGTTCTTGAAAAAGACCTTGAAACAGCTCAAGCTGAAAACGCTAAGTACAAAGAACAAT 900
                ************************************************************

TA4             TAGCTAAACAAG 912
321 324A        TAGCTAAACAAG 912
341 4291B       TAGCTAAACAAG 912
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Fig. 2. Multi-alignment of our isolate (TA4) and other two strains of *Streptococcus canis* (321 324A and 341 4291B), generated using CLUSTALW version 2.1 (http://clustalw.ddbj.nig.ac.jp/).

912 bp) was closely related to *scm* from other two Sc strains: 321 324A (accession no. KF662395.1) and 341 4291B (accession no. KF662396.1) (Fig. 2). Multilocus sequence typing (MLST) was performed by cross-referencing the sequences of 7 housekeeping genes (*gki*, *gtr*, *murI*, *mutS*, *recP*, *xpt*, and *yqiZ*) from our isolate with those registered into the Sc MLST database (http://pubmlst.org/scanis/). The isolate was found to be a sequence type (ST) 9 strain, possessing the allelic profiles 3, 5, 3, 3, 1, 2, and 3 for each of the seven genes, respectively.

Antimicrobial susceptibility assays revealed that the Sc isolate was susceptible to penicillin, cephalosporin, tetracyclines (TCs), glycopeptides, lincomycins, sulfamethoxazole/trimetoprim, chloramphenicol, and fluoroquinolones. Susceptibility to macrolides was mixed, as the isolate was susceptible to erythromycin but not

to azithromycin: its susceptibility was intermediate. It should be noted, however, that the breakpoints of antibiotic concentrations used to determine susceptibility were those for viridans group streptococci, since no breakpoints for Sc are described in the Clinical and Laboratory Standards Institute guidelines. While this susceptibility testing suggested that the isolate might be resistant to azithromycin, our PCR-based results indicated that this isolate did not possess the macrolide/lincosamide (ML) resistance genes, *erm*(A), *erm*(B) or *mef*(A) [5].

Discussion

To the best of our knowledge, this is the first reported human case of uncomplicated bacteremia caused by an ST9 Sc harboring the *scm* gene. The M-like protein expressed by the *scm* gene is a novel virulence factor with possibility of anti-phagocytic activity. Additionally, this protein acts cooperatively with enolase to bind to the C-terminal mini-plasminogen region of plasminogen, recruiting the latter to the bacterial surface and enhancing the transmigration and survival of the bacterium [2,4]. However, not all Sc strains isolated from animals possess the *scm* gene; one study detected the *scm* gene in only thirteen of nineteen strains examined (68.4%) [4]. Consistent with this result, a separate study found that 90.0% of canine and 83.3% of feline Sc strains harbored the M-like protein [6]. In this study, it was not possible to isolate and identify the Sc strain directly from the pet dog of the patient, since the dog died from the illness while the patient was hospitalized, and we need to confirm the presence of the *scm* gene among Sc strains prospectively recovered from companion animals in Japan.

The MLST method for typing Sc strains has been established [7], and ST9 was found to be the most prevalent type among the 85 Sc isolates (23/85; 27.1%), including among strains originating in humans ($n = 5$). According to information in the MLST database, ST9 strains are isolated from cats, dogs, and cows from Germany, Portugal, and the US. Reported sources of ST9 Sc isolates were skin and soft tissue exudate, vaginal exudate, ear exudate, urine, and others. Several human infections with the ST9, the prevalent ST, originating from Portugal, are registered into the database; the tissue sources of infection were skin and soft tissue exudate, respiratory tract secretions, and blood specimens. The human cases caused by other STs 2, 3, 4, 12, and 14 also originated in Portugal and the US. In this case study, we describe a human infection with a pathogenic ST9 Sc strain harboring the *scm* gene, and in future it will be interesting to analyze the relationship between the presence of the *scm* gene and the ST of the Sc strains isolated from companion animals and humans in Japan.

The isolate in this case did not possess the ML-resistance genes, *erm*(A), *erm*(B), or *mef*(A), although azithromycin was not effective against this bacterium. Previously, resistance rates of 27% against TC and 10.8% against ML were reported among 37 Sc strains isolated from dogs between 2000 and 2005 [8]. Additionally, the presence of the resistance genes *tet*(M) or *tet*(O) alone, or combinations of resistance genes [*tet*(M)/*tet*(L), *tet*(L)/*tet*(S), and *tet*(O)/*erm*(B)] have been detected in TC-resistant SC isolates ($n = 23$; resistance rate, 27%) [7]. Therefore, ML- and/or TC-resistance should be considered when antimicrobials are found to be ineffective in veterinary clinical practice.

Sc infection is rare, but host characteristics linked to susceptibility to infection, including the immunity, have been described previously. In humans, underlying medical conditions, particularly diabetes mellitus, can increase the susceptibility, as can a compromised immune system [9,10]. On the other hand, the presence of virulence factors could enhance the potential infectivity with Sc; we have described the presence of the M-like protein virulent factor in this case, but it is possible that other virulent factors might enhance Sc pathogenesis in immunocompetent individuals, and their investigation using comprehensive approaches including genome sequencing [11] and proteomics will be important in the future.

The entry site of Sc into human host should also be considered. Most cases of Sc infection, except for dog bites, originate in pre-existing wounds and skin ulcers [12,13]. Notably, however, Ohtaki and colleagues recently reported the first documented human case of sepsis caused by Sc without a dog bite in Japan [14]. While the entry mechanism remains unclear, we speculate that the pathogenic Sc, which may be resident at/around the oropharynx, skin, genitourinary tract, and anal tract, seem to invade the host through invisible wounds on human skin [15,16].

Conclusion

Companion animals kept in households are hugely important to individuals of all ages in Japan, so much so that some human hospitals have introduced Animal-Assisted Therapy to improve the mental health of human patients. Therefore, when presented with feverish patients who maintain close contact with these animals, clinicians should consider infection with Sc as well as with *Pasteurella* sp., *Prevotella* sp., and *Capnocytophaga* sp. Furthermore, since an animal's life is completely controlled by its human owner, the "One Health" concept, which recognizes that human health and animal health are connected [17], should be employed to study the crosstalk concerning bacteria, including Sc, that infect both humans and animals, to maintain their future health.

Informed consent

The patient gave his informed consent before this article was written.

Conflict of interest

The authors have disclosed no relevant financial relationships.

Ethical approval

Ethical approval was not required for this study.

Acknowledgments

The authors wish to thank Ms. Haruno Yoshida (Laboratory of Infectious Diseases, Kitasato Institute for Life Sciences & Graduate School of Infection Control Sciences, Kitasato University) and Ms. Junko Sano (Laboratory of Microbiology, Tokyo Saiseikai Central Hospital) for their assistance. This study made use of the *Streptococcus canis* MLST website (http://pubmlst.org/scanis/), which was developed by Keith Jolley with funding from the Wellcome Trust (Jolley & Maiden 2010, BMC Bioinformatics, 11:595) and is maintained by the University of Oxford.

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