








CASE SERIES

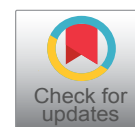
Invasive Diseases Due to Fatal *Staphylococcus caprae* Infection: A Case Series and Literature Review

Antonio Mastroianni, MD^{1*} , Sonia Greco, MD¹ , Valeria Vangeli, MD¹ , Maria Vittoria Mauro, MD²  and Roberto Manfredi, MD³ 

¹Infectious & Tropical Diseases Unit, Annunziata Hub Hospital, Cosenza, Italy

²Microbiology & Virology Unit, Annunziata Hub Hospital, Cosenza, Italy

³Institute of Infectious Diseases, Alma Mater Studiorum University of Bologna, Bologna, Italy



*Corresponding author: Dr. Antonio Mastroianni, Infectious & Tropical Diseases Unit, Annunziata Hub Hospital, Azienda Ospedaliera di Cosenza, Viale della Repubblica s.n.c, 87100 Cosenza, Italy, Tel: +39-0984-68-18-33; +39-349-54-44-330

Abstract

We report a case series of fatal invasive diseases due to *Staphylococcus caprae*. We describe the first cases of *S. caprae* sepsis in two Italian patients. In the first patient there was also evidence of the fourth case reported in the English language literature of mitral endocarditis. We also discuss the main features of differential diagnosis on the basis of a literature review.

Keywords

Staphylococcus caprae, Coagulase-negative *Staphylococcus*, Infective endocarditis, Staphylococcal sepsis, Fatal brain thromboembolism, Native valve endocarditis

Introduction

Staphylococcus caprae belongs to the broad family of coagulase-negative Staphylococci (conS), and is a potential colonizer of human skin. Initially isolated from goat milk, it has been sufficiently characterized from a bacteriological point of view since the year 1995 [1-11], although some unexpected features like the possible production of *S. aureus*-like enterotoxins deserve further studies [7,12,13].

Although showing a mild virulence potential, its biofilm (slime) production and its unpredictable antimicrobial susceptibility profile [2,4,5] make it a rare, but challenging pathogen especially in nosocomial settings [11,14-16] or when prosthetic devices are of concern, with bone and joints as the most frequently reported localizations [1,6,10,17-22].

Although sporadic episodes of otitis, mastoiditis, meningitis, endophthalmitis, urinary tract infection, pneumonia, and peritonitis have been described, usually after surgery or interventional procedures, as well as very infrequent cases of sepsis or bacteremia remain very rarely reported (Table 1) [23,24]. Reports of endocarditis are even more rare [24,25], and are usually related to prosthetic valves or implanted electronic devices (IED). The only report of *S. caprae* native valve mitral endocarditis is that described by Kwok, et al. [25].

Cases

A 68-year-old male suffering from a compensated type 2 diabetes mellitus and multiple comorbidities (COPD, diabetes-related nephropathy and a previous CNS vascular disease with severe neurological remnants including hemiplegia and dysarthria), accessed the Emergency Room of our Hospital due to altered mentation, low back pain, and an overwhelming acute heart failure with pleural-pericardial effusion. A transesophageal chest ultrasonography disclosed an endocarditis with 1.5 cm diameter vegetation on a trilobated valve, conditioning a severe left atrial-ventricular dysfunction (ejection index 40%). A CNS scan did not show further abnormalities, when compared with the previous one obtained 7 months before. Routine laboratory examinations addressed a moderate leukocytosis with neutrophilia, and increased serum C-reactive and procalcitonin levels (65.9 mg/dL and 0.97 ng/mL respectively). Multiple consecutive

Table 1: Isolation of *Staphylococcus caprae* from blood cultures.

Refences, Patient sex/ year	Patient, sex, year	Underlyin' condition	Antibiotic susceptibility	Disease	Complications	Treatment	Outcome
Vandenesch, et al. [1]	A 46-year-old man	None		MV IE	None	Cardiac surgery + 2 weeks of vancomycin	Recovery
Spellerberg, et al, [27]	A 2-day-old neonate	Congenital heart disease	R to PEN, AMP; S to: OXA, CEF, ERY, OFL, VAN	Sepsis	None	Cardiac surgery + antibiotic therapy: 14 days of cefotiam	Recovery
Kini, et al. [23]	A 30-year-old African American woman p	None	R to PEN, AMP; S to: AMPS, CLI, CEP, ERY, GEN, IMI, OXA, RIF	Nosocomial sepsis	None	Antibiotic therapy: vancomycin→CFZ	Recovery
Kwork, et al. [25]	A 76-year-old man	None		MV IE	A subacute small vessel infarct	Antibiotic therapy: 6 weeks of FLU.	Recovery
R. Hammami, et al. Tunisia, 2020 [24]	N.A.	N.A.	N.A.	MV IE	Acute coronary syndrome	N.A.	N.A.

Abbreviations: MV: Mitral Valve; IE: Infective Endocarditis; R: Resistant; S: Sensitive; PEN: Penicillin; AMP: Ampicillin; AMPS: Ampicillin/Sulbactam; CLI: Clindamycin; CEP: Cephalotin; ERY: Erythromycin; GEN: Gentamicin; IMI: Imipenem; OXA: Oxacillin; RIF: Rifampin; CEF: Cefotiam; OFL: Ofloxacin; VAN: Vancomycin; FLU: Flucoxacil; CFZ: Cefazolin

blood cultures allowed the growth of *Staphylococcus caprae*, while urine cultures tested negative. The microbial strain proved phenotypically susceptible to clindamycin, daptomycin, rifampicin, tetracycline, glycopeptides, linezolid, tigecycline and cotrimoxazole, and resistant to oxacillin, gentamycin, erythromycin, and levofloxacin. A diagnosis of defined aortic endocarditis was therefore posed, according to the modified Duke criteria. A SARS-CoV-2 disease was excluded, and the surveillance nasal and rectal swabs proved negative for colonizations. Combined i.v daptomycin (at 350 mg day), plus tigecyclin at 100 mg/day after a 100 mg loading dose), were started plus supportive therapy. A concurrent spondylodiscitis was excluded by a MRI examination of the spine, while a brain MRI scan did not show signs of metastatic infectious foci. Both ophthalmologic and odonto-stomatologic consultancies were recommended, together with the appropriate instrumental assessments. After the 6-week attack antibiotic therapy, a de-escalation schedule based on oral rifampicin-tetracycline therapy was suggested, but our patient did not survive an acute-on chronic heart ischemic attack, when still hospitalized at the intensive Cardiology Unit of our Hospital.

A 54-year-old male already suffering from a macrocephaly due to an Arnold-Chiary syndrome and a permanent ventriculo-peritoneal shunt, experienced an acute subarachnoideal hemorrhage after a head trauma occurred at home. Through the Emergency Room he was hospitalized at the Neurosurgical Department

of our Hospital, where he received neurosurgical decompression of a large right temporal subdural hematoma, confirmed by a brain CT scan, which also allowed a correct positioning of a cranial drainage. Laboratory assessment obtained upon admission did not show relevant abnormalities save a moderate increase of serum creatinkinase level (404 U/L), related to the recent trauma. Oral, nasal, and rectal surveillance swabs tested negative for all searchable microorganisms, while blood culture repeatedly yielded *S. caprae*, which proved susceptible to all tested antibiotic compounds. Intravenous dexamethasone, mannitol, furosemide therapy was immediately started to contain brain edema, together with phenobarbital-levetiracetam to prevent seizures. The standard preoperative antibiotic prophylaxis with cefazolin was followed by co-amoxiclavulanate, and subsequently switched to linezolid at 600 mg/d, which guarantees an excellent brain penetration. Despite neurosurgery and the intensive management, our patient went to death after 5 sole days since hospitalization.

Discussion

The first described case is extremely challenging due to: its clinical differential diagnosis with arterial coronary disease [22] and spondylodiscitis [18], both rare but already described occurrences in the setting of *S. caprae* infection. Both complications have been expected by us, but were carefully ruled out in our patient with appropriate clinical and instrumental examinations. The neurological signs and symptoms

following the thromboembolism from the ascertained aortic endocarditis were more difficult to be recognized timely, due to the concurrent, severe remnants of our patient who already had a very high risk of ischemic heart-cerebral disease. They were hindered by the sequelae of a previous stroke documented by appropriate imaging techniques.

Moreover, both the potential nosocomial source and bacterial colonization, both frequent underlying conditions in other studies [4,5,8,9,11,15,16,24,25], and the resort to invasive procedures as frequent proxys for *S. caprae* disseminated human disease, were excluded or absent in our setting, respectively.

Other interesting aspects which deserve further investigation are those related to colonization and intra species competition of *S. caprae* with other Staphylococci on the human skin, especially in hospital settings [4,5,8,9,16,26], an those related to the *in vivo* antibiotic effectiveness [1,4,5,8], which could not be addressed in our patient, because of his death due to an acute-on chronic heart failure. It is conceivable that our second patient described for a severe and fatal *S. caprae* sepsis contracted the staphylococcal infection during his hospitalization, as this bacterium has been implicated in several nosocomial infections [23]. Together with the case described here, three of four isolations of *S. caprae* from blood cultures were associated with cardiac malformations or endocarditis [1,24,25]. In a Indian study performed to speciate coagulase-negative staphylococci (CoNS) and their antibiotic susceptibility pattern isolated from clinical samples, among the 120 consecutive CoNS strains isolated from various clinical samples, *S. caprae* accounted for 5% (6 isolates) of all isolates (4, 66.6%, from blood). All *S. caprae* isolates from this study were susceptible to doxycycline, linezolid, and teicoplanin, and vancomycin. The resistance percentage to ciprofloxacin, gentamicin and cotrimoxazole was 33.33%. The highest methicillin resistance was in *S. caprae* (66.67%), *S. epidermidis* (64.71%), *S. lugdunensis* (57.1%) [28].

In one other study evaluating the ability of automated ribotyping to identify isolates of CoNS species obtained from the blood of hospitalized patients during a 4-year period, among 177 CoNS isolates, the collection of clinical isolates comprised 3 isolates of *S. caprae* [29].

In conclusion, we briefly report and discuss a unique case of native valve aortic endocarditis due to *S. caprae*, the only complicated by a lethal cerebral thromboembolism, in absence of colonization and resort to surgery or invasive procedures. Also *S. caprae* should be considered in the setting of severe, complicated, and potentially lethal endocarditis, and prevention measures like colonization screening promoted in hospital settings.

Author Contributions

All the authors contributed to the clinical evaluation of the cases and to the drafting of the manuscript.

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Conflicts of Interest

None.

Patient's Consent

A signed informed consent for publication was obtained, and the manuscript is in accordance with the institution's ethics committee.

References

- Wandenesch F, Eykin SJ, Bes M, Meugnier H, Fleurette J, et al. (1995) Identification and ribotypes of Staphylococcus caprae isolates isolated as human pathogens and from goat milk. J Clin Microbiol 33: 888-892.
- Tian F, Li J, Li F, Tong Y (2021) Characteristics and genome analysis of a novel bacteriophage IME1323_01, the first temperate bacteriophage induced from Staphylococcus caprae. Virus Res 305: 198569.
- Zhao J, Ma M, Zeng Z, Yu P, Gong D, et al. (2021) Production, purification and biochemical characterisation of a novel lipase from a newly identified lipolytic bacterium Staphylococcus caprae NCU S6. J Enzyme Inhib Med Chem 36: 248-256.
- Smith JT, Andam CP (2021) Extensive horizontal gene transfer within and between species of coagulase-negative Staphylococcus. Genome Biol Evol 13: evab206.
- Watanabe S, Aiba Y, Tan XE, Li FY, Boonsiri T, et al. (2018) Complete genome sequencing of three human clinical isolates of Staphylococcus caprae reveals virulence factors similar to those of *S. epidermidis* and *S. capitis*. BMC Genomics 19: 810.
- D'Ersu J, Aubin GG, Mercier P, Nicollet P, Bémer P, et al. (2016) Characterization of Staphylococcus caprae clinical isolates involved in human bone and joint infections, compared with goat mastitis isolates. J Clin Microbiol 54: 106-113.
- Kim E, Yang SM, Won JE, Kim DY, Kim DS, et al. (2021) Real-Time PCR method for the rapid detection and quantification of pathogenic Staphylococcus species based on novel molecular target genes. Foods 10: 2839.
- Slany M, Vanerkova M, Nemcova E, Zaloudikova B, Ruzicka F, et al. (2010) Differentiation of Staphylococcus spp. by high-resolution melting analysis. Can J Microbiol 56: 1040-1049.
- Kawamura Y, Hou XG, Sultana F, Hirose K, Miyake M, et al. (1998) Distribution of Staphylococcus species among human clinical specimens and emended description of Staphylococcus caprae. J Clin Microbiol 36: 2038-2042.
- Shuttleworth R, Behme RJ, McNabb A, Colby WD (1997) Human isolates of Staphylococcus caprae: Association with bone and joint infections. J Clin Microbiol 35: 2537-2541.
- Ortega-Peña S, Franco-Cendejas R, Salazar-Sáenz B, Rodríguez-Martínez S, Cancino-Díaz ME, et al. (2019) Prevalence and virulence factors of coagulase negative Staphylococcus causative of prosthetic joint infections in an orthopedic hospital of Mexico. Cir Cir 87: 428-435.

12. Weir D, Jones C, Ammerman L, Dybdahl K, Tomlinson S (2007) Report of a strain of *Staphylococcus caprae* with the genes for enterotoxin A and enterotoxin-like toxin type P. *J Clin Microbiol* 45: 3476-3477.
13. Miyahira RF, Santos EA, Leão RS, de Freitas-Almeida AC, Queiroz ML (2018) Antimicrobial susceptibility and enterotoxin-encoding genes in *Staphylococcus* spp. recovered from kitchen equipment from a university hospital in Rio de Janeiro, Brazil. *Microb Drug Resist* 24: 995-1001.
14. Rodríguez Fernández L, Martín Guerra JM, Dueñas Gutiérrez CJ (2020) Role of *Staphylococcus caprae* in nosocomial infection. *Enferm Infecc Microbiol Clin (Engl Ed)* 38: 455-456.
15. Ross TL, Fuss EP, Harrington SM, Cai M, Perl TM, et al. (2005) Methicillin-resistant *Staphylococcus caprae* in a neonatal intensive care unit. *J Clin Microbiol* 43: 363-367.
16. Paharik AE, Parlet CP, Chung N, Todd DA, Rodriguez EI, et al. (2017) Cell Host Microbe. Coagulase-negative staphylococcal strain prevents *Staphylococcus aureus* colonization and skin infection by blocking quorum sensing. *Cell Host Microbe* 22: 746-756.e5.
17. Darrieutort-Laffite C, André V, Leautez S, Tanguy G, Cormier G (2013) *Staphylococcus caprae* arthritis. *Med Mal Infect* 43: 131-132.
18. Fan Z, Yang Y, Li D, Fei Q (2020) A rare lumbar pyogenic spondylodiscitis caused by *Staphylococcus caprae* with initial misdiagnosis: Case report and literature review. *BMC Surg* 20: 200.
19. Gowda A, Pensiero AL, Packer CD (2018) *Staphylococcus caprae*: A skin commensal with pathogenic potential. *Cureus* 10: e3485.
20. Seng P, Barbe M, Pinelli PO, Gouriet F, Drancourt M, et al. (2014) *Staphylococcus caprae* bone and joint infections: A re-emerging infection? *Clin Microbiol Infect* 20: 1052-1058.
21. Rodríguez-Lucas C, Iriberry I, García-Arenzana JM, Fernández J (2019) Septic arthritis caused by *Staphylococcus caprae* following arthroscopic meniscus tear repair in a patient without any foreign device. *Enferm Infecc Microbiol Clin (Engl Ed)* 37: 421-422.
22. Hilliard CA, El Masri J, Goto M (2017) *Staphylococcus caprae* bacteraemia and native bone infection complicated by therapeutic failure and elevated MIC: A case report. *JMM Case Rep* 4: e005112.
23. Kini GD, Parris AR, Tang JS (2009) A rare presentation of sepsis from *Staphylococcus caprae*. *Open Microbiol J* 3: 67-68.
24. Hammami R, Ben Ali ZA, Charfeddine S, Abid L, Kammoun S (2020) *Staphylococcus caprae* infective endocarditis complicated by acute coronary syndrome. *Med Mal Infect* 50: 531-533.
25. Kwok TC, Poyner J, Olson E, Henriksen P, Koch O (2016) *Staphylococcus caprae* native mitral valve infective endocarditis. *JMM Case Rep* 3: e005065.
26. Ogura K, Furuya H, Takahashi N, Shibata K, Endo M, et al. (2022) Interspecies regulation between *Staphylococcus caprae* and *Staphylococcus aureus* colonized on healed skin after injury. *Front Microbiol* 13: 818398.
27. Spellerberg B, Steidel K, Lütticken R, Haase G (1998) Isolation of *Staphylococcus caprae* from blood cultures of a neonate with congenital heart disease. *Eur J Clin Microbiol Infect Dis* 17: 61-62.
28. Bora P, Datta P, Gupta V, Singhal L, Chander J (2018) Characterization and antimicrobial susceptibility of coagulase-negative staphylococci isolated from clinical samples. *J Lab Physicians* 10: 414-419.
29. Carretto E, Barbarini D, Couto I, De Vitis D, Marone P, et al. (2005) Identification of coagulase-negative staphylococci other than *Staphylococcus epidermidis* by automated ribotyping. *Clin Microbiol Infect* 11: 177-184.