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Once a Known Veterinary Pathogen, Now a Forgotten Zoonosis. Case Report of An Invasive *Staphylococcus intermedius* Group Infection

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Abstract

Introduction: *Staphylococcus intermedius* group (SIG), a known veterinary pathogen with the potential for zoonotic human infections, comprises *S. intermedius*, *S. pseudintermedius*, and *S. delphini*, which are not easily distinguishable. Without the proper equipment and procedures, it cannot be distinguished from *Staphylococcus aureus* (SAu), which causes underestimation of its true incidence.

Case Presentation: A 52-year-old male with diabetes presented with complaints of fever and malaise. He developed respiratory failure and altered mental status; hence, intensive care was provided to him. Blood cultures and bronchoalveolar lavage culture developed methicillin-resistant SIG. Despite rapid adjustment of empiric antibiotic therapy, he died of multiple organ failure.

Conclusions: Incorporating knowledge about this new pathogen and its aggressiveness into daily clinical practice can, through a high index of suspicion and detailed anamnesis, reduce misdiagnoses.

Keywords: *Staphylococcus intermedius*, Dog, *Staphylococcus aureus*, Zoonoses, *Staphylococcal infections*, Methicillin Resistance

1. Introduction

Staphylococcus intermedius group (SIG) (1), which contains the bacteria *S. intermedius*, *S. pseudintermedius*, and *S. delphini* (2), is a coagulase-positive catalase-positive subset of the genre *Staphylococcus*, that exhibits beta-hemolysis on blood agar plates (3) and is commonly isolated in dogs (4), pigeons, visons, cats, horses, foxes, racoons, and goats (5).

Although differentiation between the three pathogens is possible with equivocal microbiological algorithms that use tests such as arginine-dehydrolase and mannitol fermentation, it is mainly carried out with techniques such as matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (1, 6).

At a population level, SIG presents as a rare and transient member of skin and mucosal flora in humans. However, it can be frequently identified among dog owners and veterinary practitioners (5). Moreover, it has shown a pathogenic role in skin, and soft tissue wound infections (2, 3) - particularly in dog bite wounds- and has recently shown potential for rare invasive infections. Nevertheless, the true incidence of SIG in human wounds is probably underestimated due to its misclassification for *Staphylococcus aureus* (SAu) (2, 3) and case reports of invasive infections -endocarditis, catheter-associated infections, pneumonia, mastoiditis, sinusitis, and brain abscesses- are scarce (5).

We aim to present a case report of an invasive presentation of this pathogen that sheds light upon its high barrier for suspicion, driven by the underrecognition of its clinical importance.

2. Case Presentation

A 52-year-old male rural worker in contact with little and big animals, with a diagnosis of type 2 diabetes mellitus without treatment adherence, was admitted to the hospital. He reported 5 days of fever and malaise and presented with a symmetric cutaneous rash, temporally related to β-lactam antibiotic ingestion. Later on, during hospitalization, he complained of new-onset generalized myalgias. He had a history of potential exposure to rodent excretes at his workplace, which alerted physicians of the possibility of leptospirosis.

At the Emergency Department, the patient was febrile at 38.5°C, and his blood pressure and heart rate were 140/80 mmHg and 110 bpm, respectively. He initially required low supplemental oxygen with an inspired fraction of oxygen

of 28%, reaching a pulse oximetry $SatO_2$ of 96%. Physical examination revealed right-lower lobe pulmonary crackles at inspiration, without further relevant findings.

Blood samples were taken for cultures and routine blood investigations, apart from HIV and leptospirosis serologies (Table 1). In addition, a chest x-ray was performed that indicated atypical community-onset pneumonia (Figure 1A), and ceftriaxone was started at a dose of 1g every 12 hours.

Two days after arrival, he developed respiratory failure requiring admission to the intensive care unit (ICU) for frequent monitoring but without need for invasive mechanical ventilation (IVM) at first. At the time, he presented with bilateral pulmonary crackles, correlated to findings on a new chest x-ray (Figure 1C) and a posterior chest computed tomography (Figure 1D), which showed nodules in both lungs.

The Microbiology Laboratory informed bacterial growth in both blood culture bottles within 10 hours of incubation in a BacT/ALERT© (bioMérieux, US) automated microbial identification system. After the positive result, a sample was transferred to a solid growth medium, and catalase-positive Gram-positive Staphylococci colonies were identified.

Thus, the treating physicians added vancomycin at a dose of 1 g every 12 hours to empiric antibiotic treatment, suspecting SAu as the etiologic bacteria. With this presumptive diagnosis, a transthoracic echocardiogram was performed, with no evidence of vegetations. Afterward, the Microbiology Laboratory identified the etiologic bacteria as *S. pseudintermedius* through the VITEK® 2 Compact (bioMérieux, US) automated identification and antibiotic susceptibility testing system.

This result was manually confirmed with a positive pyrrolidonyl arylamidase enzyme (PYR) test as well as a positive O-nitrophenyl-β-D-galactopyranoside (ONPG) test and a negative Voges-Proskauer test. Methicillin resistance was detected with an oxacillin disk diffusion test. Due to an altered mental status and hypoxemia-driven high ventricular rate auricular fibrillation, he required orotracheal intubation for IMV during the ICU stay. In the process, mini-bronchoalveolar lavage fluid was obtained for culture, which later allowed for the diagnosis of methicillin-resistant *S. pseudintermedius* pneumonia. Despite all provided interventions, the patient died due to multiple organ failure.

3. Discussion

This case report displays one of the few descriptions of invasive infection by *S. pseudintermedius*. This microorganism colonizes the nares and anal mucosa of healthy cats and dogs, but it is also recognized as a veterinary pathogen (4, 6). Moreover, SIG is recognized as an infectious agent (7), particularly in special populations -namely people of old age as well as those with diabetes or immunodepression (3).

In a retrospective case series of 81 patients with SIG infections, only 7% reported contact with dogs, allegedly due to the under-registry of epidemiological data in clinical files. In 60% of investigated cultures in such series, the result was polymicrobial, failing to discriminate between the clinical characteristics of those patients with monomicrobial cultures versus those with polymicrobial cultures. Therefore, the clinical importance of SIG infections is unknown in polymicrobial settings (3).

Detailed clinical history with adequate epidemiological data recollection, with emphasis on occupational exposures, is key to our ability to elaborate papers of quality about these bacteria's true incidence and dominant clinical presentations.

Adding complexity to the problem, SIG and SAu, apart from sharing clinical scenarios and risk factors, share morphological similarities that derive from frequent misclassifications of one for the other. This is the case, in particular, of settings without automatic microbiological identification systems (3); or without personnel with appropriate training and standardized algorithms for microbial identification (2). Therefore, true incidence cannot be ascertained until after these obstacles have been sorted out.

On top of that, cefoxitin disk diffusion tests, which are used to evaluate methicillin resistance in SAu, provide equivocal results with SIG when compared to results obtained with oxacillin tests. Hence, either ignorance about this fact or the misclassification of one organism for the other (3, 6), could derive from the premature de-escalation of antibiotics and poor clinical results. It is noteworthy that, despite the relatively low reported incidence of methicillin-resistance in SIG, the specimen isolated from our patient had a positive oxacillin test, as a surrogate for methicillin, without resistance to other investigated antibiotics.

In our center, we have only had four clinical isolates of SIG throughout last year, three of which were from blood cultures and one from a breast abscess. This is probably a reflection of the low rate of the culture of community-acquired skin and soft tissue infections in our hospital

Table 1. Complementary Examinations Performed at Different Stages of the Patient's Hospitalization

Variables	Admission to General Ward	Admission to Intensive Care Unit	Final stage of Hospitalization in Intensive Care Unit
Hemoglobin (g/dL)	16.8	14.0	13.8
White blood cells (cells/mm^3)	16.380	18.000	18.300
Neutrophils (%)	94.9	90.1	92.3
Platelet count (plat/L)	201.000	81.000	42.000
Urea (mg/dL)	49	66	75
Creatinine (mg/dL)	0.57	0.46	2.1
Sodium (mEq/L)	132	133	128
Potassium (mEq/L)	4.05	4.71	5.1
Glycemia (mg/dL)	316	219	310
AST (U/L)	60	57	81
ALT (U/L)	37	38	56
ALP (IU/L)	136	148	160
Total bilirubin/direct bilirubin (mg/dL)	0.47	0.48	2.5
CK (U/L)	992	-	-
Albumin (g/dL)	2.04	-	-
Lactate (mg/dL)	-	30.8	-
pH	-	7.36	7.26
pCO_2 (mmHg)	-	35.5	53.9
pO_2 (mmHg)	-	98	62.7
HCO^{3-} (mmHg)	-	19.8	23.9
Supplemental oxygen	FiO_2 28%	FiO_2 50%	Mechanical ventilation in prone position
Serologies	Hantavirus: negative; Leptospirosis: negative; HIV: negative; Syphilis: negative; Hepatitis B: negative		
Ecocardiography	Slight increase in left atrium diameter; No vegetations; Ejection fraction 65%; Grade I mitral insufficiency		

since most SIG isolates reported in the literature are from such samples (1, 3). In the case of our patient, the initial clinical diagnosis was that of community-acquired pneumonia. However, the epidemiological suspicion of leptospirosis, due to the contact of the patient with rodent excretes and the fact that this infection is endemic in our region, justified its investigation, although it was subsequently negative.

After that, complementary examinations, Gram stain results, and the torpid course of illness raised the suspicion of SAu bacteriemia; therefore, led us to adjust the empiric antibiotic therapy.

Although SIG pneumonia complicated with bacteriemia, which was the final diagnosis, never occurred to us in the list of differential diagnoses, the high standards of care of our Microbiology Laboratory and its fast results permitted the prompt arrival at such diagnosis. Nevertheless, it remains a question whether the first 48 hours without an appropriate antibiotic therapy was determinant for the patient's demise, or if the course of the disease was marked solely by the pathogen's aggressiveness.

3.1. Conclusions

Incorporating and producing knowledge about SIG infections, which can resemble SAu infections clinically and microbiologically, together with an exhaustive anamnesis, including detailed data about patients' occupational and non-occupational exposures, will allow for fewer diagnostic mistakes involving this pathogen, therefore isolating SIG incidence from that of SAu.

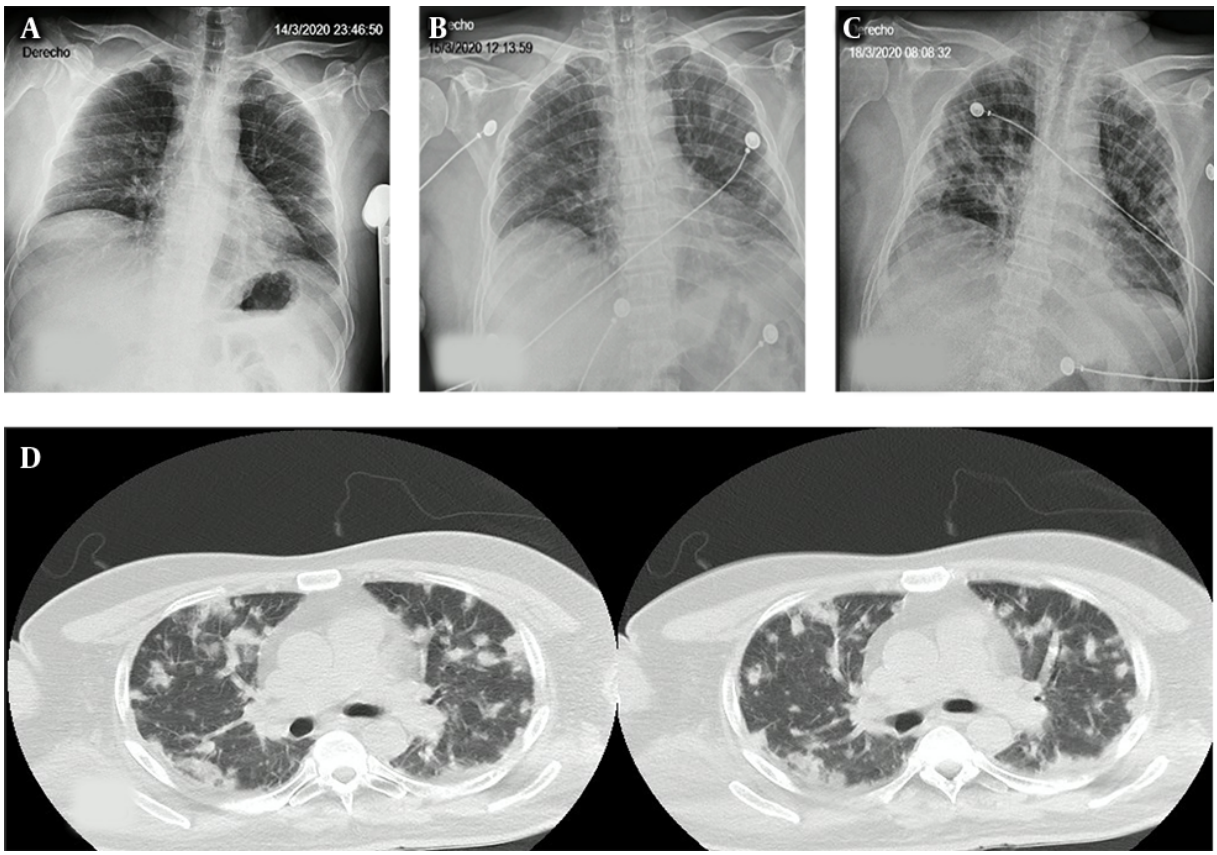

Figure 1. A, chest X-Rey at admission with interstitial infiltrates; B, chest X-Rey with accentuation of interstitial infiltrates; C, chest X-Rey at ICU admission with new bilateral alveolar infiltrates; D, chest CT with nodular bilateral infiltrates, along with areas of consolidation.

Footnotes

Authors' Contribution: Both authors were part of the medical team in charge of the patient and participated in the conception of the case report. L.U. took charge of acquiring a copy of the clinical files, chest X-ray and CT. They both reviewed the literature and drafted the document, while M. C. revised the paper. After the final version of the document was ready, they approved it and agreed to the accountability of the presented paper's accuracy and integrity.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: The case report was approved by the hospitals authorities, which provided access to the patients files, and its ethical board. Due to the nature of this article, they did not produce an ethical approval code.

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Informed Consent: The patient's family gave express consent to the publication of this document and to the usage of his medical files, provided that his identity was preserved

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