Spondylodiscitis and bacteremia due to *Staphylococcus hyicus* in an immunocompetent man

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Abstract

Introduction *Staphylococcus hyicus* is a coagulase-variable *Staphylococcus* spp. well-known by veterinarians since it is the major agent of a severe cutaneous infection in piglets called exudative epidermitis. In other species the symptoms of infection are quite different. Human cases are uncommon but seem to occur more frequently after repeated contacts with farm animals.

Case report We report the case of a 58-year-old man suffering from debilitating subacute lumbar pain, in whom diagnosis of infectious spondylodiscitis was based on spine MRI and positive microbiological results. A strain of *S. hyicus* was surprisingly isolated from blood cultures and bone biopsy. Identification was confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker, USA), and the patient was successfully cured with a six-week course of anti-staphylococcal antibiotic regimen.

Conclusion The prevalence of *S. hyicus* in human clinical samples is very low, but may be underestimated. This pathogen may enter the bloodstream through a skin injury, and then induce various pyogenic manifestations in people working with farm animals. *S. hyicus* exfoliative toxins, responsible for dermatological lesions in piglets, seem unable to damage the human epidermis, explaining the absence of cutaneous blisters in the previously reported cases. Precise data about its pathogenicity in humans and the adequate therapy are lacking.

Keywords Spondylodiscitis, coagulase-variable *Staphylococcus*, *Staphylococcus hyicus*

Introduction

Staphylococcus hyicus is a coagulase-variable *Staphylococcus* spp., usually isolated from animals

and mainly responsible for skin lesions in piglets. The scarcity of reported cases of human infection, combined with variable biochemical properties of this germ in routine identification tests, mainly concerning coagulase activity, may favor misdiagnosis. We report here a rare case of *S. hyicus* osteoarticular infection and bacteremia in an immunocompetent man.

Case report

A 58-year-old man was admitted to the hospital for intense backache. His medical past history was remarkable for recurrent left radiculopathy linked with facet joint arthrosis and disc herniations from L3 to S1. Three years previously he had undergone two epidural infiltrations, followed by lumbar radiofrequency thermocoagulation with good results. Two months prior to admission he had experienced a recurrence of acute debilitating lumbar pain, and a CT of the spine only showed the already known and non-progressive degenerative lesions. Given this unexplained excruciating pain he was then

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hospitalized for further investigations. The patient denied fever or weight loss over the previous six months. On admission vital parameters were as follows: body temperature 37.7 °C, blood pressure 150/89 mmHg, heart rate 101 bpm. His chief complaint was intense lumbar pain, evaluated 8/10 on visual analogue scale, radiating beyond the left knee and preventing him from walking. Palpation of the cervical and thoracic spine was painless, but we found tenderness over the last lumbar vertebrae, and bilateral Lasègue sign. Peripheral reflexes were unaffected and there was no neurological deficit or sphincter incontinence. Cutaneous examination only showed a few recent scratches on his hands, without sign of superinfection. The rest of the physical examination revealed no sign suggestive of endocarditis or embolic event. The sole remarkable routine laboratory result was an elevated C-reactive protein (77.2 mg/L), but erythrocyte sedimentation rate hadn't been measured. Prostatic specific antigen level was within normal ranges. MRI showed both a L3-L4 lateral disc herniation and signs of spondylodiscitis affecting the same vertebrae, without paravertebral or epidural abscess. Technetium-99m-methylene diphosphonate bone scintigraphy also confirmed a single abnormal fixation at L3-L4 level, and transthoracic echocardiography revealed no valvular lesion or abscess. Despite apyrexia, blood cultures were sent on arrival, but yielded negative results, as well as serological testing for *Coxiella burnetii*, *Bartonella* spp. and *Brucella* spp. Eventually surgical biopsies were taken on L4 for bacteriological and histological analysis, followed by additional blood cultures to increase the likelihood of identifying a causative microorganism. In the absence of severe sepsis or neurological complication empiric antibiotic therapy wasn't started immediately after sampling. The following days two separately collected aerobic and anaerobic blood cultures, then the biopsy specimen, grew white and grey small colonies of non-aureus *Staphylococcus* (negative PASTOREX™ STAPH-PLUS test, Bio-rad, Hercules, CA). The pathology results of the bone biopsy showed only a few signs of

inflammation (mainly edema and fibrin deposits) but no granuloma or malignant cells. Contamination of samples by several coagulase-negative *Staphylococcus* strains was initially suspected, but biochemical tests identified a single strain of *S. hyicus*. This strain was mainly characterized as follows: white and grey small non-hemolytic colonies, easier growth in aerobic than anaerobic atmosphere, presence of catalase and alkaline phosphatase activities, aerobic acid production from α -lactose and saccharose, but not from maltose or mannitol. Results were then confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS, Bruker, Billerica, MA, USA). Antibiotic susceptibility testing showed a fully susceptible microorganism, with a minimum inhibitory concentration for oxacillin < 0.25 mg/L (Vitek2 P631 cards, bioMérieux, Marcy-l'Étoile, France). Because of a cloxacillin supply disruption, intravenous cefazolin (2 g TID) plus gentamycin (5 mg/kg daily, during three days) were started. On day ten, after a good clinical response, alleviation of pain and immobilization by a lumbar brace, the patient was discharged under oral levofloxacin (500 mg BID) and rifampicin (900 mg daily), since the diagnosis of endocarditis had been considered unlikely. We discovered on this occasion that our patient used to raise apparently healthy chickens and doves for his personal supply. Considering the initial favorable outcome, and the absence of paravertebral or epidural abscess, antibiotics were administered for six weeks, without significant side effects. Clinical evaluation at the end of treatment revealed constant apyrexia and very significant pain relief. A concomitant control MRI however showed a worsening of radiological features (almost complete destruction of the L3-L4 intervertebral disc and increased gadolinium enhancement of L3 and L4 vertebral bodies), but without soft tissues invasion. Finally no additional antibiotic treatment was prescribed. About three months after discontinuation of the antibiotic therapy the patient underwent another clinical assessment, during which he presented a good general condition and no sign of relapse.

Discussion

We describe a rare case of *S. hyicus* spondylodiscitis and bacteremia in a man who raised farm animals. This Gram-positive coccus was initially named *Micrococcus hyicus*, then later classified among the genera *Staphylococcus* and designated *S. hyicus*.^{1,2} It is a coagulase-variable species, since only some strains possess coagulase activity. The small number of reported *S. hyicus* human infections, together with its variable coagulase synthesis, can make routine biochemical identification challenging.^{2,4} This may justify confirmation with MALDI TOF MS or PCR techniques.⁴

S. hyicus is mainly encountered in veterinary medicine. It belongs to the commensal flora of several animals, including pigs, chickens, or cows,² but is better known as a major agent of exudative epidermitis in piglets, a potentially lethal disease characterized by exfoliation of the skin, blisters formation and brown serous exudation.^{1,5} It is also involved in subclinical mastitis in cows, skin infections in horses or donkeys, ophthalmological diseases in poultry or rare cases of osteoarticular infections in pigs, heifers, turkeys or falcons.^{2,5,6} To our knowledge only four previous human infections with *S. hyicus* have been published. In 1988 Aliu described a series of toxic shock syndromes, including one in a boy, due to *S. hyicus*.⁷ This germ was then isolated in a case of cellulitis after a donkey bite,⁸ and during a bacteremia and foot cellulitis in a breeder of piglets.⁴ More recently it has been involved in a case of neonatal septicemia in Saudi Arabia.⁹ Of note, including ours, three out of five cases occurred among farmers or people who owned cattle, and the presumed contamination route was inoculation of *S. hyicus* through damaged skin.

S. hyicus infections can be fatal in animals, especially in piglets. Data available from such infections have shown that the major virulence factors of *S. hyicus* are exotoxins, such as enterotoxins and exfoliative toxins. Six exfoliative toxins, able to induce exudative epidermitis in piglets, have been isolated from certain strains of *S. hyicus*, and characterized to date: ExhA, ExhB, ExhC, ExhD, *Staphylococcus hyicus* exfoliative

toxin B (ShETB) and *Staphylococcus hyicus* exfoliative toxin A (ShETA). The four Exh toxins and ShETB are serine proteases that show a high homology of amino acid sequence with the exfoliative toxins ETA, ETB and ETD of *S. aureus*.¹⁰ This homology of amino acid sequence is particularly marked in the proximity of their active site,¹⁰ which explains that they all have similar pathophysiological functions in animals and humans respectively. Concerning ShETA, phylogenetic analysis showed it isn't related to the same serine protease group of exfoliative toxins, but has similarities with ETC of *S. aureus*.¹⁰ *S. aureus* ETA, ETB and ETD are involved in the pathophysiology of two blistering skin diseases in humans: bullous impetigo and staphylococcal scalded skin syndrome. They are indeed able to selectively target desmoglein-1, a desmosomal adhesion molecule synthesized by the keratinocytes.¹¹ Desmoglein-1 is expressed throughout the epidermis. However, in the superficial layers of the skin it is a major protein responsible for cell-to-cell attachment, whereas in the deep epidermis other adhesion molecules are coexpressed, such as desmoglein-3 and E-cadherin, both resistant to lysis by *S. aureus* exfoliative toxins. As a consequence when these toxins selectively cleave desmoglein-1, the blisters only occur in the upper stratum spinosum of the epidermis, where the molecular function of desmoglein-1 isn't compensated.¹¹ Likewise, Exh toxins of *S. hyicus* target porcine desmoglein-1-equivalent, inducing separation of the keratinocytes in the granular layer and causing exudative epidermitis in piglets.¹² Exh toxin production wasn't sought in our case. However Exh toxins of *S. hyicus* and ETA, ETB and ETD of *S. aureus* show species specificity, meaning that Exh toxins of *S. hyicus* can't digest human desmoglein-1 or induce epidermitis-like syndromes in humans.¹² We can indeed notice that the four aforementioned patients, as well as ours, didn't seem to suffer from blistering lesions.

Spondylodiscitis can occur from two main contamination routes: hematogenous spread or direct external inoculation during invasive procedures such as spinal surgery or epidural infiltrations. In our patient in contact with

animals, *S. hyicus* spondylodiscitis likely resulted from embolic complications of a bacteremia that followed an unnoticed skin wound. He indeed didn't remember being recently injured. The location of the infection is also consistent with this hypothesis, since hematogenous pyogenic spondylodiscitis affect the lumbar vertebrae in 50 to 60% of cases.¹³

It could also be assumed that inoculation of *S. hyicus* into the spine occurred three years before during the lumbar invasive treatments. Indeed although this microorganism isn't a common inhabitant of human flora, and despite the fact that we didn't look for a skin carriage of *S. hyicus* in our patient, this bacteria has already been identified on human skin.¹⁴ However, the limited destruction of vertebral endplates and the absence of soft tissues invasion don't seem compatible with a three-years incubation period, even for a mild strain of non-*aureus* *Staphylococcus*.

This strain of *S. hyicus* was very susceptible to commonly used antibiotics, and the minimal inhibitory concentration for oxacillin was below 0.25 mg/L. However recommendations for oxacillin breakpoints for coagulase-variable *Staphylococcus* spp. involved in human infections are lacking. We therefore decided to base the antibiotic regimen on national guidelines of treatment of methicillin-susceptible *S. aureus* spondylodiscitis and bacteremia. Initial intravenous treatment associated cefazolin, in the absence of cloxacillin, and a short course of gentamycin. After ten days of parenteral therapy, it was replaced by oral antibiotics, given the clinical improvement, the lack of elements suggestive of endocarditis, and the susceptibility of the strain to several highly bioavailable molecules, which also achieve high concentrations in bones. Given the lack of significant interactions with the patient's co-mediations, we prescribed the combination levofloxacin and rifampicin, which is recommended as first-line therapy. Under this regimen we observed a favorable clinical and laboratory response, and the follow-up MRI confirmed the absence of late-onset damages in epidural and paravertebral soft tissues. Concerning the bones however, MRI changes on

L3 and L4 worsened with an increase of gadolinium enhancement, and a severe decrease in the L3-L4 intervertebral disc height. No root compression or spinal instability was found. Recent literature data currently suggest that worsening of MRI features is frequently observed during the early follow-up of spondylodiscitis, even in patients who respond well to antimicrobial therapy.^{13,15} As a consequence, in our patient with complete pain relief and normalization of inflammatory markers, these MRI changes were not considered as a failure of medical treatment. Antibiotic therapy wasn't prescribed beyond six weeks, and no surgical management was proposed at this stage. To date, no signs of relapse have been noticed during the three-months follow-up.

Conclusion

S. hyicus invasive infections are rare in humans, but may be underdiagnosed especially in people in close contact with farm animals. *S. hyicus* identification can be challenging, which requires clinicians and bacteriologists to be vigilant, to avoid misdiagnosis in front of infections with non-*aureus* *Staphylococcus* in farmers or veterinarians. This could also help collect more data about the virulence of *S. hyicus* in humans, its antibiotic resistance pattern, and the appropriate therapy.

Consent: Written consent was obtained from the patient prior to publication.

Authors' contributions statement: MF, ML and AE were in charge of the patient while hospitalized. MF FD and ML wrote the case report. BL contributed to the identification of the microorganism. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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