Erysipelothrix rhusiopathiae bacteremia without endocarditis: rapid identification from positive blood culture by MALDI-TOF mass spectrometry. A case report and literature review

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Abstract

Erysipelothrix rhusiopathiae is a Gram-positive bacillus that is infrequently responsible for infections in humans. Three forms have been classified: a localized cutaneous form (erysipeloid) caused by traumatic penetration of *E. rhusiopathiae*, a generalized cutaneous form and a septicemic form. The latter type of disease has been previously associated with a high incidence of endocarditis. Here we report a case of *E. rhusiopathiae* bacteremia in a 74-year-old man, probably started from an erysipeloid form, in which endocarditis did not develop. This case presents some particular and uncommon features: i) no correlation with animal source; ii) correlation between bacteremia and erysipeloid lesion; iii) absence of endocarditis. MALDI-TOF mass spectrometry allowed to obtain a rapid identification (within 4 hours from bottle positivity) of *E. rhusiopathiae*. Together with direct antimicrobial susceptibility testing, this approach could improve the rate of appropriate therapy for bloodstream infections due to this fastidious pathogen.

Introduction

Erysipelothrix rhusiopathiae is a Gram-positive bacillus that is infrequently responsible for infections in humans. Human disease, although rare, can originate from animal or environmental sources. To this regard, animal sources are often associated with occupational exposure (butchers, fishermen, fish handlers, veterinarians), with pigs as the most important reservoir.[1] On the other hand, soil, food scraps and water contaminated by infected animals represent the most common environmental sources. The organism is widespread and occurs in decomposing organic matter. Notably, *E. rhusiopathiae* can survive in soil for several weeks.[2] Human disease is classified into three forms: a localized cutaneous form (erysipeloid) caused by traumatic penetration of *E. rhusiopathiae*, a generalized cutaneous form and a septicemic form. The latter type of disease has been previously associated with a high incidence of endocarditis. In a previous study concerning invasive infection cases since 1912, it was reported that about 90% of cases of *E. rhusiopathiae* bacteremia result in endocarditis.[3] This association has been recently questioned, since some cases of *E. rhusiopathiae* bacteremia without subsequent endocarditis have been reported in the most recent literature.[4-8] Here we report a case of *E. rhusiopathiae* bacteremia, probably started from an erysipeloid form, in which endocarditis did not develop. Furthermore, we used the PubMed Database to search for recent case reports of bloodstream infections caused by *E. rhusiopathiae*.

Case Report

An Italian citizen (male, 74 years old) presented to the emergency department of the San Leopoldo Mandic Hospital in Merate (Lecco, Italy) on August, 2014. The patient was in treatment with oral anticoagulant therapy due to cardiopathy and cerebral vasculopathy. On admission, he had a low grade fever (38.4°C), hearth rate 100 beats per minute, blood pressure 125/75 mm of Hg, white blood cell count 4.2×10^9/L. In addition, he showed difficulty in his movement due to a polymorphic erythema on the right leg characterized by well-defined and raised borders with a localized edematous skin portion and reddening. Based on laboratory and clinical data (modified early warning score = 4), the presence of sepsis was suspected.[9] Together with other interventions (as appropriate for sepsis condition), two blood cultures were performed and sent to the laboratory where they were promptly incubated in the BacT/ALERT instrument (bioMérieux, Marcy l'Etoile, France). No biological samples from leg were sent to the microbiology laboratory. Therapy with ceftriaxone (1 g twice daily) plus azithromycin (500 mg daily) was then initiated. The patient recalled that the lesion, then classified as erysipelas, had been present for about two months. No contact with animals were reported. However, physicians observed that the patient lived in non-optimal hygienic conditions. After a 48 h incubation period, an aerobic bottle from blood cultures performed at the emergency department was flagged positive by the BacT/ALERT instrument (bioMérieux). Direct microscopic examination based on Gram staining evidenced the presence of Gram-variable rods. Bacterial identification was performed directly from positive blood culture bottle by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (VITEK MS, bioMérieux) using the following procedure. An aliquot (2.5 mL) of the blood culture was transferred in a tube with gel separator (BD Vacutainer® Blood Collection Tubes, Becton, Dickinson and Company, Milan, Italy) and centrifuged at 3500 rpm for 10 minutes. The supernatant was discarded and the pellet was inoculated on two blood agar plates incubated at 36°C in O_2 and 5% CO_2, respectively. After a short term incubation period (4 hours), microbial identification was obtained by the VITEK MS directly from bacterial growth on agar plates. Microorganisms recovered from agar plates were directly applied to VITEK MS target slide in duplicate (two spots for each isolate) and were covered with one microliter of CHCA (α-Cyano-4-hydroxycinnamic acid) matrix.

E. rhusiopathiae was identified according to the observation of Gram-variable rods as obtained by Gram staining. Next to rapid identification with VITEK MS, a suspension, adjusted to a 0.5 McFarland turbidity standard, was created directly from bacterial growth and used for direct antimicrobial susceptibility testing by Etest strips (bioMérieux) using the Mueller-Hinton Fastidious agar (bioMérieux).

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The minimum inhibitory concentrations of 7 antibiotics were evaluated, including penicillin G, cefotaxime, imipenem, ciprofloxacin, levofloxacin, clindamycin, and vancomycin. Since no specific criteria were available for *E. rhusiopathiae*, results were arbitrarily interpreted according to EUCAST criteria and non-species related breakpoints.[10]

As shown in Table 1, antimicrobial agents used for empirical treatment resulted highly active against the etiological agent isolated from blood. A transesophageal echocardiography did not reveal valve vegetation. Ten days after admission, the patient was discharged without fever and in good conditions. The follow-up conducted seven months after discharge showed good clinical conditions (taking into account his underlying illness). The erysipelas on the right leg was completely cured.

Discussion and Conclusions

This report describes a case of *E. rhusiopathiae* bacteremia without endocarditis in an immunocompetent patient, successfully treated with ceftriaxone plus azithromycin, presumably started from a localized skin form.

Similar cases are overall uncommon. Table 2 summarizes clinical features of *E. rhusiopathiae* invasive case reports, searched in the most recent literature using the PubMed Database (only articles in English have been taken into account).[3-35]

With respect to previous reports, our case presents some particular and uncommon features. First, erysipelas is most often caused by *Streptococcus pyogenes* or *Staphylococcus aureus*, less so by group B, C or G streptococci.[11] For this reason, *Erysipelothrix* infections are considered uncommon and especially non-occupational cases are very rare. In our case the patient lived in non-optimal hygienic conditions but he had not been in contact with any animal, so the source of infection could be the soil contaminated by the microorganism and the infection could occur by traumatic penetration in the skin through tiny breaks. Overall, a total of 32 cases (including our case) have been recently reported. Of importance, our search revealed only two other cases associated to poor hygienic conditions (in addition to our case), while an exposure to animal sources was mostly present (Table 2).

Second, bacteremic infection, with or without endocarditis, was previously considered most commonly a primary infection rather than dissemination from localized cutaneous lesion.[1,5,12] In contrast to this assumption, the recent literature shows an increasing rate of bacteremic infections started from localized cutaneous lesion (Table 2). Particularly, in our case, bacteremia developed subsequently an erysipeloid lesion.

Third, *E. rhusiopathiae* bacteremia is most commonly associated with severe clinical illness and is often complicated with endocarditis.[1] More than one half of patients with systemic infection had predisposing factors such alcohol or drug dependence, immunosuppression, and chronic liver disease (Table 2). Furthermore, our search showed that more than one third of the patients (34.4%) with invasive *E. rhusiopathiae* infections developed endocarditis (Table 2). This rate is much lower than that reported by Gorby and Peacock, in which about 90% of cases of *E. rhusiopathiae* bacteremia result in endocarditis.[3] However, in contrast to these evidences, in our case the patient did not present any of these clinical features and no involvement of the endocardium was detected.

It is noting that bacteremic *E. rhusiopathiae* infection may occur more commonly than reports suggest. It may be under-diagnosed and under-reported because the resemblance it bears to other infections and the problems that may be encountered in isolation and identification of this pathogen. Furthermore, Gram-positive rods cultured from blood are often dismissed as difteroids and not fully identified.

In our case, bacteremia without involvement of endocardium was resolved by treatment with ceftriaxone plus azithromycin. To this regard, penicillins and cephalosporins are the first line of choice for treating *E. rhusiopathiae* infections (see also Table 2) while this pathogen is naturally resistant to vancomycin, teicoplanin, daptomycin, gentamicin, netilmicin, polimyxin B, tetracycline and trimethoprim/sulfamethoxazole.[1] It is worth noting that some of the latter antimicrobial agents are commonly used as empirical therapy for treatment of suspected sepsis. Thus, early diagnosis of all forms of *E. rhusiopathiae* infection appears to be essential, especially in the case of endocarditis.

Of note, although *E. rhusiopathiae* is usually highly susceptible to penicillins and cephalosporins, all death patients described in Table 2 had been treated with such beta-lactam antibiotics. Based on data collected from the recent literature (Table 2), the overall mortality rate for bacteremia was 12.5%. Three out of four deaths occurred in patients with endocarditis, whereas the remaining occurred in a patient with sepsis and oropharyngeal cancer. A previous study reported a mortality rate of 38% in patients with *E. rhusiopathiae* endocarditis.[3] In our search the mortality rate for *E. rhusiopathiae* endocarditis accounted for 27.3% (Table 2). This rate may partly be explained by the use of vancomycin, often in combination with gentamicin, in the empirical therapy of endocarditis in patients who are allergic to penicillin and infected with Gram-positive microorganisms.[1] With respect to available alternative drugs, susceptibility data for quinolones are very rare in the literature.[4,6,19] In our case, we observed very low MIC values for ciprofloxacin and levofloxacin (Table 1), thus suggesting that these drugs could represent a valid therapeutic option, at least for patients with known allergy to beta-lactams, particularly if at risk of infectious endocarditis (*i.e.* patients with heart valve prosthesis).

The introduction of mass spectrometry in clinical microbiology laboratory has notably improved identification of microorganisms at the species level. To our best knowledge, this is the first report in which identification of *E. rhusiopathiae* has been performed directly from positive blood culture bottle by MALDI-TOF mass spectrometry. Identification by mass spectrometry and direct antimicrobial susceptibility testing performed on positive blood culture can provide results about 24 hours earlier than routine standard methods. This approach could allow to reduce the duration of empirical treatment and improve the rate of appropriate therapy for bloodstream infections caused by this fastidious pathogen.

Table 1. Susceptibility profile of *Erysipelothrix rhusiopathiae* blood isolate.

Antimicrobial agent	MIC (mg/L)	Interpretation
Penicillin G	0.004	S
Cefotaxime	0.094	S
Imipenem	0.008	S
Ciprofloxacin	0.094	S
Levofloxacin	0.064	S
Clindamycin	0.094	S
Vancomycin	64	-

Based on EUCAST criteria and non-species related breakpoints.[10] No interpretation criteria are available for vancomycin.

Table 2. Characteristics of bloodstream infections caused by *Erysipelothrix rhusiopathiae* as obtained by case reports described in the recent literature.

Authors	Sex, age	Type of infection	Underlying illness/risk factors	Contact with animals/rural setting	Treatment	Outcome
Gorby & Peacock[3]	M, 67	Skin erythema, bacteremia	Chronic alcohol abuser, cirrhosis	Farming activity	PENRecovered	
Cascio *et al.*[4]	F, 53	Infected trunk, arm and leg ulcer, bacteremia	Hepatitis C, cirrhosis	Uncooked meat consumption	LEV	Recovered
Kichloo *et al.*[5]	M, 64	Abdominal pain, bacteremia	Chronic alcohol abuser, cirrhosis, hypertension, diabetes mellitus	Uncooked meat consumption	PENRecovered	
Drekonja[6]	M, 59	Cellulitis, bacteremia	None	Gardening activity	MOX	Recovered
Upapan & Chayakukeeree[7]	NA	Psoas abscess, osteomyelitis, bacteremia	Cirrhosis, diabetes mellitus	NA	Surgery, NA	Recovered
Birlutiu[8]	M, 54	Skin erythema, bacteremia	Chronic lymphocytic leukemia, hepatitis B bronchopneumonia	Fish consumption	PEN	Recovered
Townshend *et al.*[13]	F, 52	Bacteremia	Bronchitis	Contact with uncooked fish	PEN	Recovered
Ognibene *et al.*[14]	M, 58	Septic shock	Diabetes mellitus, myocarditis	Fishing activity	PEN, CLI, GEN	Recovered
Normann & Kihlstrom[15]	M, 53	Skin erythema, bacteremia	None	Butcher activity	PEN, NET	Recovered
Quabeck *et al.*[16]	M, 79	Skin erythema, pericarditis, bacteremia	None	Hunting activity	PEN	Recovered
Shumak *et al.*[17]	M, 53	Skin erythema, septic bursitis, bacteremia	Chronic lymphocytic leukemia	Farming activity	ERY, TOB	Recovered
Callon & Brady[18]	M, 61	Bacteremia	Chronic alcohol abuser, intestinal perforation	None	CET	Recovered
Venditti *et al.*[19]	M, 70	Skin erythema, endocarditis, bacteremia	None	Farming activity	PEN, TPL, Surgery	Died
García-Restoy *et al.*[20]	F, 18	Skin erythema, bacteremia	Systemic lupus erythematosus	Occasional contact with animals	PEN, AMX	Recovered
Schuster *et al.*[21]	F, 28	Bacteremia	Chronic alcohol abuser, pancreatitis	None	PEN	Recovered
Fakoya *et al.*[22]	F, 43	Cellulitis, bacteremia	Chronic alcohol abuser	Gardening activity	None	Recovered
Fernández-Crespo *et al.*[23]	M, 51	Skin erythema, bacteremia, endocarditis, renal failure	Chronic alcohol abuser	Contact with uncooked meat/fish	PEN, Surgery	Died
Thomas *et al.*[24]	F, 29	Endocarditis, bacteremia	Systemic lupus erythematosus	None	PEN, CEF	Recovered
Totemchokchyakarn *et al.*[25]	F, 43	Skin erythema, bacteremia	Systemic lupus erythematosus	Contact with uncooked meat	CEF, AMX	Recovered
Jones & Khoosal[26]	F, neonate	Infection contracted during delivery	Prematurity, hepatosplenomegaly	Poor hygienic condition at birth	CTX, AMK	Recovered
Nandish & Khardori[27]	M, 78	Endocarditis, bacteremia	Chronic alcohol abuser	Uncooked meat consumption	PEN, Surgery	Recovered
Sheng *et al.*[27]	M, 32	Bacteremia	Oropharyngeal cancer	Colonization of the oral cavity	AMC	Died
Artz *et al.*[29]	M, 46	Skin erythema, endocarditis, bacteremia, septic arthritis	Chronic alcohol abuser	Butcher activity	AMC, CLI, Surgery	Recovered
Romney *et al.*[30]	F, 67	Lumbar spondylitis, bacteremia	Diabetes mellitus	Fish consumption	PEN	Recovered
Ko *et al.*[31]	F, 63	Skin erythema, endocarditis, bacteremia, multiple brain infarctions	Hepatitis B, chronic alcohol abuser	Fishing activity	PEN, CRO	Recovered
Mahavanakul *et al.*[32]	M, 44 F, 50 F, 42	Skin erythema, endocarditis, bacteremia (3 out of 3)	Cirrhosis (case 1); Diabetes mellitus, nephrotic syndrome (case 2); Dialysis (case 3)	Farming activity (cases 1 and 2); None (case 3)	PEN, CAZ (case 1); CAZ (case 2); CAZ, CLA (case 3)	Died (case 1); Recovered (cases 2 and 3)
Surrun *et al*[33]	F, 67	Cellulitis, septic shock	Diabetes mellitus, hypertension, ischemic heart disease	Contact with uncooked fish	CTX, CLO	Recovered
Joo *et al.*[34]	F, 63	Meningitis, endocarditis, bacteremia	Systemic lupus erythematosus	None	CRO, VAN, AMP, Surgery	Recovered
Campbell & Cowan[35]	M, 51	Skin erythema, endocarditis, bacteremia	Remote history of heroin abuse	Poor hygienic condition	SAM	Recovered
This report	M, 74	Infected arm ulcer, bacteremia	Cardiopathy, cerebral vasculopathy	Poor hygienic condition	CRO, AZI	Recovered

AMC, Amoxicillin/clavulanate; AMK, Amikacin; AMP, Ampicillin; AMX, Amoxicillin; AZI, Azythromycin; CAZ, Ceftazidime; CEF, Cefazolin; CET, Cephalotin; CLA, Clarithromycin; CLI, Clindamycin; CLO, Cloxacillin; CRO, Ceftriaxone; CTX, Cefotaxime; ERY, Erythromicin; GEN, Gentamicin; LEV, Levofloxacin; MOX, Moxifloxacin; NET, Netilmicin; PEN, Penicillin; SAM, Ampicillin/sulbactam; TOB, Tobramycin; TPL, Teicoplanin; VAN, Vancomycin; NA, not available.

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