J Infect Chemother 25 (2019) 816–819

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

Yokenella regensburgei necrotizing fasciitis in an immunocompromised host

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ARTICLE INFO

Article history:
Received 22 February 2019
Received in revised form
17 March 2019
Accepted 26 March 2019
Available online 17 April 2019

Keywords:
Yokenella regensburgei
Necrotizing fasciitis
Skin and soft-tissue infection

ABSTRACT

We report a case of necrotizing skin infection caused by *Yokenella regensburgei* in an immunosuppressed patient with orthotopic liver transplantation. Initial bacterial culture identification was suggestive of *Hafnia alvei*. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) confirmed identification of *Y. regensburgei*. Necrotizing fasciitis is potentially fatal and requires aggressive management, including early diagnosis, appropriate antibiotic selection, and operative debridement.

1. Introduction

One of the less frequently encountered members of the family *Enterobacteriaceae* causing human disease is the genus *Yokenella*. The genus, composed of a single species *Y. regensburgei*, has been previously known by a number of acronyms and heterotypic synonyms including Japanese National Institute of Health biogroup 9, Centers for Disease Control Enteric Group 45, and *Koserella trabulsii* [1–3]. *Y. regensburgei* phenotypically resembles *Hafnia alvei* and has rarely been implicated in syndromic disease such as bloodborne infections and wounds ranging from cellulitis to soft tissue infection. Very little information is presently available regarding potential risk factors, disease presentations, pathogenicity, and treatment outcomes associated with this species. In the present case report we provide the first description of *Y. regensburgei* causing a life-threatening wound infection (necrotizing fasciitis) in an immunocompromised host.

2. Case report

In August 2018, a 64-year-old female from Pennsylvania on immunosuppression therapy (Sirolimus 1mg and prednisone 1mg once daily) for orthotopic liver transplantation due to alcoholic cirrhosis [Child-Turcotte-Pugh Class B (moderately severe liver disease)] experienced abrupt onset of right lower extremity swelling, excruciating pain, and multiple areas of purpuric lesions [Fig. 1A]. Two days earlier, she had participated in outdoor gardening activities with mushroom compost fertilization sustaining a small right leg cutaneous puncture due to a rose bush. The patient was afebrile on admission with maximum temperature of 36.6 °C. Clinical exam was unremarkable except her right leg skin lesions as described. Laboratory results demonstrated serum neutrophilic leukocytosis of 15.5 cells/mcL [ref: 3.9–9.5 cells/mcL], creatinine of 2.40 mg/dL [ref: 0.40–1.20] baseline 1.0 mg/dL, creatine phosphokinase (CPK) 833 U/L [ref: 0–200], aspartate aminotransferase (AST) 120 U/L [ref: 11–35], alanine aminotransferase (ALT) 76 U/L [ref: 10–60], alkaline phosphatase (AP) 73 U/L [ref: 30–110], total bilirubin (Tb) 1.6 mg/dL [ref: less than 1.1], albumin 1.9 g/dL [ref: 3.4–4.6]. While the serum erythrocyte sedimentation rate (ESR) was 11 mm/h [ref: 0–20 mm/h], high-sensitive C-reactive protein (CRP) was significantly elevated at 14.0 mg/dL [ref: 0.1–1.0]. She was empirically treated with vancomycin (15 mg/kg intravenous every 24-h), cefepime (1 g intravenous every 24-h),

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https://doi.org/10.1016/j.jiac.2019.03.025
1341-321X/

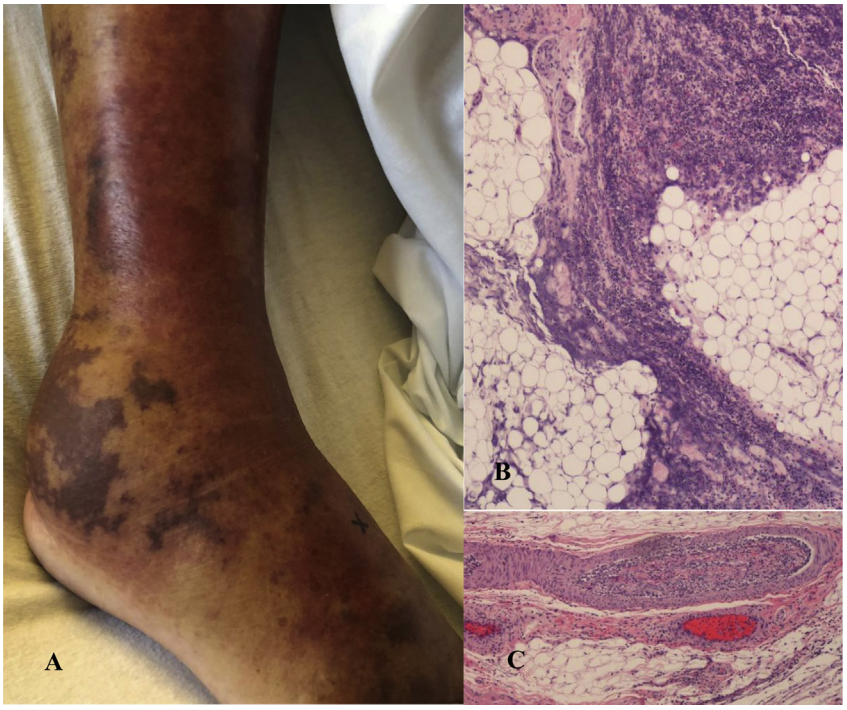

Fig. 1. A. Purpuric cutaneous lesions involving the right lower extremity and foot. **B.** Extensive neutrophilic inflammation within deep soft tissue associated with fat necrosis. **C.** Occasional intravascular fibrin thrombi. (hematoxylin and eosin stain; magnification, ×1000).

and clindamycin (900 mg intravenous every 8-h). Despite antimicrobial therapy and aggressive fluid resuscitation, she remained tachypneic and hypotensive requiring mechanical ventilation and vasopressor support. A decision for wound debridement was made upon surgical consultation. During surgery, grayish necrotic fascia, extensive subcutaneous tissue necrosis, loss of resistance of the normally adherent superficial fascia to blunt dissection, and "cloudy" dishwater fluid were noted. Deep tissue samples revealed rare WBC and occasional gram-negative rods on gram-stain. A clinical diagnosis of necrotizing fasciitis was made. Histologic examination demonstrated extensive neutrophilic inflammation within deep soft tissue associated with fat necrosis [Fig. 1B] and occasional intravascular fibrin thrombi [Fig. 1C].

Blood cultures were negative after 120 hours of incubation at 37 °C [BACTEC™ 9240; Becton Dickinson and Company, Franklin Lakes, NJ, USA]. Tissue specimens were spread onto blood and MacConkey agar plates [Becton, Dickinson and Company, Franklin Lakes, NJ]. Characteristic smooth, moist, translucent, and gray colonial morphologic findings suggestive of an *Enterobacteriaceae* species were noted on blood agar. The isolate generated a seven-digit code of 5305113 on the API 20E strip [bioMerieux, Durham, NC] yielding an identification of *Hafnia alvei* with a 99.4% confidence value. Subsequently, the same organism was tested on the BD Phoenix Automated Microbiology System [BD Diagnostic Systems, Sparks, MD] and was identified as *Y. regensburgei* with a 99.9% confidence value. The Phoenix antibiogram profile demonstrated susceptibility to ceftriaxone, cefepime, ciprofloxacin, levofloxacin, meropenem, and cotrimoxazole but resistance to ampicillin and cefazolin. Because of the discrepancy in the final identification of this isolate between the API 20E strip and the BD Phoenix system the strain was forwarded to Quest Diagnostics for matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [Bruker Daltonics, Bremen, Germany]. MALDI-TOF analysis identified the colonies as *Y. regensburgei* [identification score of 1.99 (ref: 1.7–1.9 indicates genus identification)]. A score of >1.9 is considered acceptable for species identification of gram-negative enteric bacteria [4].

The patient's condition worsened ultimately requiring above the knee amputation (AKA) due to extensive necrosis and persistent sepsis. She was treated with cefepime and clindamycin during the perioperative period. She responded well and was discharged to complete a course of rehabilitation physical therapy. On discharge, no oral antimicrobial drugs were prescribed.

3. Discussion

Y. regensburgei is an infrequently encountered member of the family *Enterobacteriaceae*. Isolates primarily belong to bacterial intestinal flora of insects and well water in the environment [1–3]. The bacterium is biochemically characterized as gram-negative, oxidase-negative, motile with a peritrichous flagella, Voges-Proskauer negative and Simmons citrate positive [1–3]. It closely resembles *H. alvei* biochemically but differs in several reactions including the Voges-Proskauer test and citrate utilization (Table 1) [5–15]. While *Y. regensburgei* is unable to produce hydroxyproline amidase, tripeptidase, or proline deaminase, these tests are not available on automated identification systems to assist with identification [9]. Identification of *Y. regensburgei* in the microbiology laboratory is problematic as in our case using commercial systems as the correct species identification rate using such systems is <80% [5]. Following resolution of two discrepancies in the study by Snyder et al. [16] the Phoenix instrument was found to have achieved an overall identification accuracy of *Enterobacteriaceae* at the genus and species levels of 100%. Citrate (Simmons) utilization and fermentation of melibiose are key tests performed by BD Phoenix ™ 100 to accurately identify *Y. regensburgei* and *H. alvei* [2,8]. Our isolate using the BD Phoenix ™ Automated Microbiology System

Table 1
Key Biochemical characteristics of *Y. regensburgei*.

Tests	API 20 E results from our case	[a]BD Phoenix ™ results from our case	[b]Expected results of *Y. regensburgei*	[b]Expected results *H. alvei*
Acid from Malonate	NP	Positive	Positive	Negative
Acid from Melibiose	Negative	Negative	Positive	Negative
Citrate utilization	Positive	Positive	Positive	Negative
Colistin resistance	NP	Resistant	Resistant	Sensitive
Voges-Proskauer	Positive	NP	Negative	Positive

NP, not performed.
[a] The BD Phoenix ™ automated identification (ID) system used in this clinical case was NMIC/ID-304 panel.
[b] Data from: Hickman-Brenner FW, Huntley-Carter GP, Fanning GR, Brenner DJ, Farmer JJ 3rd. Koserella trabulsii, a new genus and species of Enterobacteriaceae formerly known as Enteric Group 45. J Clin Microbiol 1985; 21:39–42 and Bhowmick T, Weinstein. A deceptive case of cellulitis caused by a Gram-negative pathogen. J Clin Microbiol 2013; 51: 1320-3.

identified *Y. regensburgei* with 99% probability through a series of biochemical assays.

The misidentification of *Yokenella* using the API 20E strip supports this conclusion and suggests that the extremely low frequency of *Y. regensburgei* infections reported in the literature may be partially due to this problem. 16S rRNA gene sequencing is often not discriminatory for many genera and species within the family *Enterobacteriaceae* because of high 16S sequence similarities and close phylogenetic relationships and; therefore, this assay was not performed [2,9,13,14,17]. While 16S rRNA gene sequencing is preferential over MALDI-TOF MS for definitive species identification it is not sufficient for some groups such as members of the *Enterobacteriaceae* because the genera in this family are so closely related phylogenetically that 16S rRNA gene sequencing cannot clearly distinguish each species from one another [17]. MALDI-TOF MS clearly has some limitations in species identification but mostly with gram-positive bacteria. MALDI-TOF MS compares favorably to 16S rRNA gene sequencing in gram-negative bacterial identification including unusual species [18–20]. Despite concerns from one reported case of *Y. regensburgei* infection [14], MALDI-TOF MS databases are fairly comprehensive and robust; therefore, available commercial databases are sufficiently complete to allow for efficient, routine identification.

To our knowledge, a literature review of cases revealed an association of *Y. regensburgei* infection among ten (10) patients with immunocompromised conditions. Report details of these cases are summarized in Table 2 [4–13]. Predisposing factors for infection include alcohol abuse and severe liver disease, as reviewed by Abbott and Janda [5,6], infection with human immunodeficiency virus (HIV) [7], immunosuppressive therapy [8,9], particularly with high-dose steroids, chronic kidney disease [9,10,13,15] and diabetes mellitus [8,12–14]. In the case presented here, the patient was immunocompromised secondary to her orthotopic liver transplant and use of immunosuppression therapy.

Necrotizing fasciitis caused by *Y. regensburgei* as the sole pathogen have not been reported, although Bhowmick and Weinstein [9] reported a skin and soft tissue infection that progressed rapidly and mimicked *Streptococcus pyogenes* cellulitis with lymphangitic spread in a patient with multiple myeloma and autologous stem cell transplant history. Stock and colleagues [10] demonstrated that *Y. regensburgei* were resistant in vitro to cefazolin, cefaclor, and amoxicillin-clavulanic acid, by production of Amp-C beta-lactamases, but were sensitive to all tested aminoglycosides, chloramphenicol, folate-pathway inhibitors, fosfomycin, quinolones, and tetracyclines.

In summary, this report describes the first case of *Y. regensburgei* associated necrotizing fasciitis in an immunocompromised patient

Table 2
Case Report summary of *Yokenella regensburgei* infections among immunocompromised patients.

Reference	Age/Sex	Diagnosis	Comorbidity	Specimen	Laboratory diagnosis	Treatment	Outcome
1994 [6]	74/male	Septic arthritis	ALC	Synovium	Biochemicals	AMK	Unknown
1994 [6]	35/female	Bacteremia	ALC	Blood	Biochemicals	CIP	Survived
2005 [11]	82/male	Cellulitis	CKD	Wound	Biochemicals	CIP	Survived
2008 [15]	57/male	Bacteremia, Sepsis, and urinary tract infection	CKD, DM, and heterotopic renal transplant	Blood, and urine	Biochemicals	CIP, and P/T	Survived
2009 [12]	77/male	Abdominal abscess, pneumonia and sepsis	DM, esophageal adenocarcinoma, and renal cell carcinoma	Aspirate, Blood, and sputum	Biochemicals	LVF, and P/T	Unknown
2011 [8]	42/male	Bacteremia and cellulitis	Corticosteroids, and DM	Blood	Biochemicals	CTR	Survived
2013 [9]	48/male	Cellulitis and bacteremia	CKD, corticosteroids, multiple myeloma and stem cell transplant	Aspirate and blood	Biochemicals, "partial" 16S rRNA PCR	CLI, GEN, and IPM/CS	Deceased
2015 [13]	71/male	Diabetic foot infection	CKD, and DM	Wound	Biochemicals, 16S rRNA PCR	P/T	Survived
2017 [14]	74/male	Bacteremia, and diabetic foot infection	DM	Blood, and wound	Biochemicals, MALDI-TOF, 16S rRNA PCR	A/S, and CEFT	Survived
2017 [7]	38/male	Bacteremia, and sepsis	HIV	Blood	Biochemicals	CEFOX	Survived
Our case	64/female	Necrotizing fasciitis	Orthotopic liver transplantation, and immunosuppressant	Blood, and wound	Biochemicals, MALDI-TOF	CEF, and CLI	Survived

Abbreviations: ALC, alcoholism; CKD, chronic kidney disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; A/S, ampicillin/sulbactam; AMK, amikacin; CEF, cefepime; CEFOX, cefoxitin; CCEFT, ceftazidime; CIP, ciprofloxacin; CLI, clindamycin; CTR, ceftriaxone; GEN, gentamicin; IPM/CS, imipenem-cilastatin; LVF, levofloxacin; and P/T, piperacillin/tazobactam.

that is supported by established clinical and histologic criteria [21]. As in two other reported cases [7,9], we propose this is an opportunistic pathogen from soil with the association between her gardening practice and puncture wound. Given that *Yokenella* species-related infections are uncommon, this case highlights an aggressive need to further investigate and interpret unexpected culture findings in clinical practice, particularly in the setting of immunocompromising conditions. Recognition of infections due to unusual pathogens should warrant further evaluation and appropriate management in association with an infectious disease consultation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship

WW, JU, CB, SB, and JMJ took part in the care of the patient and draft of the report. All authors meet the ICMJE authorship criteria.

Conflicts of interest

The authors declare no competing or conflicts of interests.

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