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Case Report

Necrotizing Fasciitis Caused by ESBL-Producing *Raoultella ornithinolytica* in an Immunocompromised Patient with VEXAS Syndrome

Moe Sakamoto-Tokunaga[a], Takayuki Katsuyama[a§], Masaki Matoba[a], Tomokazu Tamura[a], Natsuki Kubota[a], Yuya Terajima[a], Kenta Shidahara[a], Kei Hirose[a], Kazuya Matsumoto[a], Shoichi Nawachi[a], Takato Nakadoi[a], Yu Katayama[a], Keigo Hayashi[a], Yoshia Miyawaki[a], Eri Katsuyama[a,b], Haruki Watanabe[a], Mariko Takano-Narazaki[a], Yoshinori Matsumoto[a], Ken-Ei Sada[a,c], Shuma Tsuji[b], Kazuyoshi Gotoh[b], Shinnosuke Fukushima[d], Hideharu Hagiya[d*§], and Jun Wada[a]

[a]*Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,* [b]*Department of Medical Laboratory Science, Graduate School of Health Sciences, Okayama University,*
[d]*Department of Infectious Diseases, Okayama University Hospital, Okayama 700-8558, Japan,*
[c]*Department of Clinical Epidemiology, Kochi Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan*

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory somatic) syndrome has a poor prognosis, with infections being a major cause of death. *Raoultella ornithinolytica* is an environmental bacterium found predominantly in soil and water. Although *R. ornithinolytica* can cause various infections, necrotizing fasciitis due to this bacterium has not been reported. We describe the case of an 84-year-old Japanese male with VEXAS syndrome who developed septic shock and necrotizing fasciitis while he was under immunosuppressive therapy. The pathogen was initially misidentified as *R. planticola* by mass spectrometry but later confirmed by whole-genome sequencing as extended spectrum β-lactamase (ESBL) produced by *R. ornithinolytica*. Although a life-saving leg amputation was required, the patient recovered with appropriate antibiotic therapy. *R. ornithinolytica* is thus able to cause severe skin infections in immunocompromised individuals.

Key words: necrotizing fasciitis, *Raoultella ornithinolytica*, VEXAS syndrome, whole-genome sequence

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory somatic) syndrome is a recently described autoinflammatory monogenic disease resulting from an acquired somatic mutation in *UBA1**, an X-linked gene involved in the ubiquitin-proteasome system [1]. The syndrome is characterized by fever, pancytopenia, chondritis, vasculitis, and neutrophilic dermatitis [2]. VEXAS syndrome is associated with a high incidence of serious infection [3], and the prognosis of patients with this disease appears to be poor, with a 5-year survival rate at 63% in a French VEXAS cohort [2].

Raoultella ornithinolytica, formerly classified as *Klebsiella* spp., is a facultative anaerobic, gram-negative bacillus that is a member of the *Enterobacterales* family. It is commonly found in nature and in hospital environments [4, 5]. Although clinical cases of *R. ornithinolytica* infections have been documented elsewhere, skin and soft-tissue *R. ornithinolytica* infections are rare,

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*Corresponding author. Phone: +81-86-235-7342; Fax: +81-86-235-7345
E-mail: hagiya@okayama-u.ac.jp (H. Hagiya)
§These authors made equal contribution to this manuscript.

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with no necrotizing fasciitis reported [6]. We describe a serious case of necrotizing fasciitis induced by *R. ornithinolytica* in an elderly immunocompromised patient who was undergoing treatment for VEXAS syndrome.

Case Presentation

An 84-year-old Japanese male whose past history included unexplained systemic inflammation, neutrophilic dermatosis, purpura on the lower limbs, laryngeal edema, and interstitial pneumonia had been treated with glucocorticoids for suspected vasculitis for the past 8 years. He presented with macrocytic anemia, and during the course of that disease thrombocytopenia and leukopenia also developed. One year before the current admission, he was diagnosed with VEXAS syndrome, an adult-onset autoinflammatory syndrome characterized by a somatic mutation in the *UBA1* gene. We detected one of the common mutations of VEXAS syndrome (UBA1 121A>G: p.M41V) in the patient's peripheral blood cells. Prior to his admission, the patient had undergone treatment with glucocorticoids and weekly subcutaneous tocilizumab (162 mg), and 3 months before the admission he experienced a relapse of VEXAS syndrome; high-dose glucocorticoid therapy was initiated.

After the remission induction therapy, the daily prednisolone dose was tapered from 40 to 15 mg by the time of the present admission, and the patient was taking sulfamethoxazole/trimethoprim (sulfamethoxazole 400 mg/trimethoprim 80 mg) 1×/week to prevent pneumocystis pneumonia (PCP). He had been diagnosed with an iliopsoas abscess caused by *Streptococcus agalactiae* at ~16 months before this admission; he was treated with multiple antibiotics. He also had type 2 diabetes, managed with dapagliflozin.

On the admission day, the patient had developed a high fever and reported pain in his right lower leg, prompting an emergency call. Upon his arrival at our hospital, his vital signs were as follows: Glasgow Coma Scale, E4V2M4; body temperature, 37.2°C; blood pressure, 92/41 mmHg; heart rate, 91 beats/min; respiratory rate, 16 breaths/min; and oxygen saturation, 90% on room air. The physical examination revealed swelling and dark reddish discoloration with purpura plus needle-sized punctures with clear exudate in his right lower leg (Fig. 1A). Blood tests showed a white blood cell (WBC) count at 8,690/μl (neutrophils 89.2%, lymphocytes 9.3%) and a mildly elevated C-reactive protein (CRP) level (0.61 mg/dl), which were likely affected by the patient's treatment with tocilizumab. Plain computed tomography (CT) imaging demonstrated significant subcutaneous edema without gas formation.

The patient was diagnosed with cellulitis of the right lower limb and was started on vancomycin (VCM) and meropenem (MEPM). He was initially admitted to the general ward; however, within 5 h he developed septic shock with the following vital signs: blood pressure, 59/37 mmHg; heart rate, 128 beats/min; body temperature, 37.1°C; and oxygen saturation ranging from 85% to 92% with a nasal cannula at 3 l/min. A repeated blood test revealed an elevated WBC count at 16,500/μl and CRP level at 4.01 mg/dl, indicating a significant inflammatory response and progression of the infection (Table 1).

At 8 h post-admission, the patient was transferred to the hospital's intensive care unit (ICU) due to worsening of the sepsis. Given the rapid progression, nec-

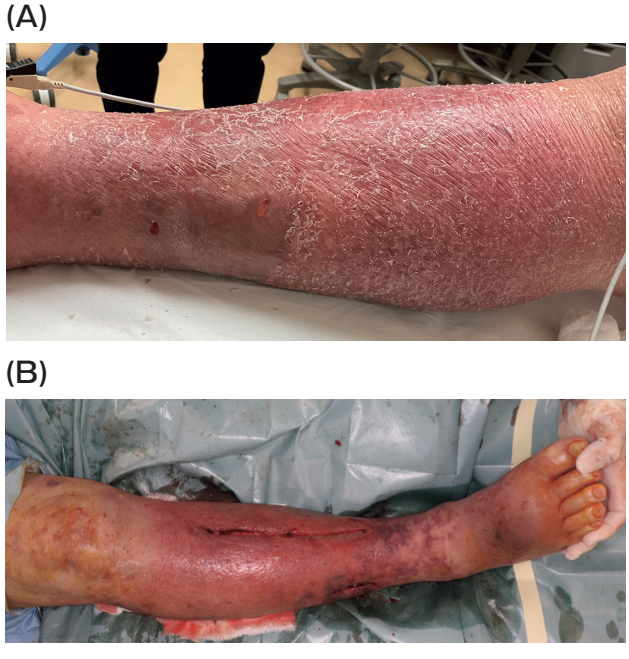

Fig. 1 Clinical appearance of the right lower leg of the patient, an 84-year-old Japanese male with VEXAS syndrome. **A**, At the initial visit. Swelling and dark reddish discoloration with purpura plus needle-sized punctures with clear exudate were observed in his right lower leg; **B**, Intraoperative findings in the right lower leg. The incisional opening of the right gastrocnemius fascia revealed a large amount of serous exudate.

rotizing fasciitis complicated with streptococcal toxic shock syndrome was suspected, and the patient underwent an emergent incision and drainage surgery, during which black necrotic tissue on the posterior aspect of the right lower leg, including subcutaneous tissue, was excised through debridement. A large volume of serous exudate was drained upon the incision and the release of the right gastrocnemius fascia (Fig. 1B). After the surgery, the patient received combinatory antimicrobial therapy consisting of MEPM, VCM, and clindamycin (CLDM), along with an intravenous immunoglobulin supplement.

Although two sets of blood cultures were negative, gram staining of the intraoperative specimens revealed the presence of gram-negative bacilli. On day 2, *Raoultella planticola* was isolated from bacterial cultures by a MALDI (matrix assisted laser desorption ionization) Biotyper (Bruker Daltonics, Billerica, MA, USA). The organism showed resistance to an array of beta-lactams including ampicillin, cefazolin, ceftriaxone, and cefepime (Dry Plate Eiken; Eiken Chemical Co., Tokyo), suggesting extended-spectrum beta-lactamases (ESBL) as a product of the *R. ornithinolytica* infection (Table 2). Based on these results, the treatment with CLDM and VCM was discontinued.

On day 11 of admission, below-knee amputation was performed by the orthopedic team to control the refractory infection. MEPM was discontinued on day 13, and the patient was discharged from the ICU on day 26. He was discharged home on day 90.

Microbiological analysis. We performed multiplex polymerase chain reaction (PCR) testing (Cica Geneus® ESBL Genotype Detection KIT 2, Kanto Chemical Industry Co., Tokyo) after DNA extraction (Cica Geneus DNA Extraction Reagent, Kanto Chemical Industry). The results indicated that the isolate harbored $bla_{\text{CTX-M1}}$ and bla_{TEM}. To further determine the bacterial species, we performed whole-genome sequencing. DNA was extracted from bacteria cultured in liquid Mueller-Hinton medium supplemented with 0.25 μg/ml MEPM at 37°C for 18 h using the DNeasy PowerSoil Pro Kit (Qiagen, Valencia, CA, USA). DNA was then sequenced using the DNBSEQ-G400RS platform (MGI Tech, Shenzhen, China). An average nucleotide identity (ANI) analysis showed high similarity

Table 1 Laboratory data

Hematology	On admission		Five h after admission	
White blood cells	8,690	/μl	16,500	/μl
Neutrophils	89.2	%	95.1	%
Lymphocytes	9.3	%	3.2	%
Hemoglobin	9.9	g/dl	8.6	g/dl
Platelets	570,000	/μl	630,000	/μl
Biochemistry				
BUN	38.9	mg/dl	39.7	mg/dl
Creatine	1.83	mg/dl	2.37	mg/dl
Total protein	4.3	g/dl	4.6	g/dl
Albumin	2.9	g/dl	3.4	g/dl
CRP	0.61	mg/dl	4.01	mg/dl
LDH	430	U/l	329	U/l
AST	56	U/l	35	U/l
ALT	141	U/l	96	U/l
Na	143	mmol/l	143	mmol/l
K	3.6	mmol/l	3.9	mmol/l
CK	48	IU/l	104	IU/l
Blood glucose	154	mg/dl		
HbA1c	7.1	%		
Coagulation				
PT-INR			1.23	
APTT			38.8	sec
FDP			<2.5	mg/ml

BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; Na, sodium; K, potassium; CK, creatine kinase; PT-INR, Prothrombin Time-International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; FDP, fibrin degradation products.

Table 2 Antimicrobial susceptibility results of ESBL-producing *Raoultella ornithinolytica*

Antibiotics	MIC	Evaluation
Ampicillin	>16	R
Ampicillin/Sulbactam	>16	R
Piperacillin/Tazobactam	4	S
Cefazolin	>4	R
Cefmetazole	<0.5	S
Ceftriaxone	<2	R
Ceftazidime	2	S
Cefepime	8	I
Ceftolozane/Tazobactam	1	S
Meropenem	<0.5	S
Levofloxacin	2	R
Gentamicin	<4	S
Amikacin	<16	S
Minocycline	<4	S
Sulfamethoxazole/Trimethoprim	>40	R
Fosfomycin	<64	S

Minimum inhibitory concentration (MIC, μg/ml) of each antimicrobial agent was examined by Dry Plate Eiken (Eiken Chemical Co., Ltd, Tokyo, Japan).

(99.4%) with the reference strain of *R. ornithinolytica* (CP138839.1).

Discussion

We have described a case of necrotizing fasciitis caused by ESBL-producing *R. ornithinolytica* during treatment with glucocorticoids and tocilizumab for VEXAS syndrome. Despite undergoing a lower-limb amputation, the patient responded well to antimicrobial therapy and intensive care management.

Infections are a major cause of death in patients with VEXAS syndrome [7], and the most common infection sites have been the lung (59%), skin (10%), and urinary tract (9%) in reported cases [3]. Risk factors for serious infections included age >75 years at VEXAS onset, arthralgia, p.Met41Val mutation, and the use of a JAK inhibitor [3], with advanced age and p.MET41Val mutation applicable to our patient's case. Importantly, VEXAS syndrome itself may confer an intrinsic immunodeficiency, as severe infections occur even in patients on low-dose glucocorticoids (*i.e.*, ≤10 mg/day) or no immunosuppressive therapy [3]. In addition, tocilizumab suppresses the increase in the CRP level, making the early diagnosis of severe infections challenging. Cases of necrotizing fasciitis in which the patient's CRP level did not increase during treatment with tocilizumab have been reported [8,9]. In our patient's case, both the underlying VEXAS syndrome and the immunosuppressive therapy with glucocorticoids and tocilizumab passively contributed to the development of severe necrotizing fasciitis.

Although *Raoultella* species were previously classified under the genus *Klebsiella*, phylogenetic studies, including 16S rRNA and *rpoB* sequence analyses, led to their reclassification as *Raoultella* in 2001 [4]. The genus *Raoultella* currently comprises three species: *R. ornithinolytica*, *R. planticola*, and *R. terrigena*. Among these species, *R. ornithinolytica* is ubiquitous in environmental sources such as soil, water, and plants and is capable of causing a range of human infections, including pneumonia, biliary or urinary tract infections, bacteremia, and sepsis [10]. *R. ornithinolytica* infections most commonly originate in the urinary tract (32%), followed by skin and soft tissue (13%) [10]. *R. ornithinolytica* also poses challenges as a nosocomial pathogen with a rising incidence of antimicrobial resistance [10-12]. The unveiled pathogenicity of *R. ornithinolytica* includes its ability to form biofilms, the production of polysaccharide capsules, and the presence of siderophore and fimbriae [6]. Our search of the relevant literature identified no prior clinical case of necrotizing fasciitis caused by *R. ornithinolytica*.

In-depth investigations into bacterial identification and antimicrobial resistance are essential for expanding the understanding of the clinical and microbiological features of *Raoultella* species infections. The pathogenic organism in the present patient's case was first reported as *R. planticola* based on a MALDI-TOF MS (time of flight mass spectrometry) analysis. However, whole-genome sequencing later revealed that the organism was *R. ornithinolytica*, with very high similarity (99.4%). Such a discrepancy highlights the importance of incorporating a molecular approach to improve the accuracy of bacterial identification in future cases.

Increased antimicrobial resistance in *R. ornithinolytica* isolates was recently described [13,14]. The ESBL genes $bla_{\text{CTX-M1}}$ and bla_{TEM} corresponding to the observed antimicrobial resistance phenotype were confirmed in our patient; however, in the absence of long-read sequencing, deeper genotyping of potential resistance mechanisms was unavailable. Clinicians should be aware of the possibility of antimicrobial resistance in *R. ornithinolytica* clinical isolates and ensure that broad-spectrum treatment is empirically initiated.

We have provided the details of a case of necrotizing fasciitis caused by *R. ornithinolytica* that developed during treatment with glucocorticoids and tocilizumab for VEXAS syndrome. Our patient's case indicates that *R. ornithinolytica* can cause severe skin and soft-tissue infections in immunocompromised individuals, highlighting the importance of precise bacterial identification.

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